The Dow Chemical Company
Midland

Confidential Offer to Compromise
Inadmissible in a Court of Law

February 1, 2007

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RE: Summary of Site-Specific Cleanup Criteria Legal Issues Meeting Held on December 20, 2006

Dear Ms. Cavanaugh and Ms. Marolf:

Thank you for taking the time to meet with Mike Robinson, Dan DeWitt and myself on December 20, 2006, to discuss some of the legal issues related to The Dow Chemical Company's development and use of site-specific cleanup criteria in conjunction with Dow's ongoing remedial investigations. The purpose of this letter is to summarize the important points of agreement from the meeting so that the parties will have a clearer path forward as they continue to work together to determine the appropriate cleanup criteria to apply in the City of Midland and in and along the Tittabawassee River.[1]

Foremost, both Dow and the State agree that the "best available information" should be used whenever possible to develop generic and site-specific cleanup criteria, as provided in Part 201, Rule 706. While there appears to be some disagreement, at least initially, regarding the flexibility afforded by the administrative code when calculating site-specific criteria, both parties agree that the regulations generally leave room for interpretation and policy determinations and so do not necessarily foreclose further discussion. In addition, some of the legal interpretation issues where there is a potential for disagreement may become moot as the Dow and MDEQ technical teams continue to work together regarding development of criteria.

[1] Please note that this letter does not attempt to summarize all of the discussion between the parties, but instead focuses on areas of agreement only. The lack of mention in this letter of any issue or argument should not be construed by either party as significant.

Therefore, it makes sense to postpone some of the legal discussions and decisions until after the technical teams have had more opportunity to work together.

Both parties are in agreement that the regulations clearly allow changes to site-specific exposure assumptions and certain chemical-physical properties, as set forth in Rule 706a(9) and (9)(a), if such changes are based on site-specific circumstances or information peculiar to the site. For example, although the generic default for Ingestion Absorption Efficiency (AEI) currently listed in the administrative rules is 50%, Dow has conducted a pilot oral bioavailability study based on site-specific information that may support a different value for the bioavailability of dioxins and furans in soil from Midland and along the Tittabawassee River. Accordingly, Dow and the State may agree on and use a site-specific value based on this site specific information.

Dow also understands that the State intends to update at least one dioxin algorithm input, as part of a larger rulemaking for application state-wide. Specifically, the State intends to revise the default dermal absorption efficiency factor (AEd) for dioxin from the current value of 3% to a new value of 1.75%, reflecting the best available information for dioxin. Although the parties understand that the rulemaking process is uncertain and subject to change, the parties agree that Dow may begin relying on this updated value now, in contemplation of the upcoming change.

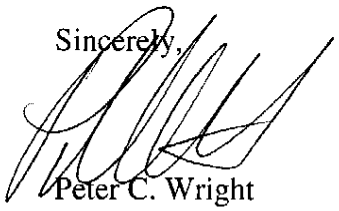
The parties also agree that Dow should use the currently-promulgated age adjusted dermal factor (DF) of 353 mg-yr/kg-day when calculating site-specific criteria. *See* Rule 706a and Rule 720. When MDEQ calculated its dioxin direct contact criterion of 90 parts per trillion (ppt), MDEQ used an age adjusted dermal factor of 2442 mg-yr/kg-day. Since that time, MDEQ has adopted and promulgated an updated dermal factor of 353 mg-yr/kg-day, which it has subsequently used for the calculation of all other direct contact criteria. The MDEQ intends to consider a rule change to the dioxin criterion to take into account the new dermal factor, if, in the end, it deems such a change is needed generally or is necessary for site-specific purposes. In the meantime, we understand that Dow may work with the new default in the development of its site-specific criteria.

Finally, the State and Dow agree that the technical teams should continue working together to evaluate the technical background for both the cancer slope factor for dioxins and furans and the non-cancer effects of dioxins and furans. Because the cancer slope factor for dioxin is currently listed as "NA" or "not available" in the administrative rules, it is Dow's understanding that the rules mean what they say and that a cancer slope factor must be calculated and used for purposes of development of site specific criteria. However, the State believes that because the MDEQ used a cancer slope value of 75,000 mg/kg-day$^{-1}$ in calculating its now-promulgated 90 ppt generic criterion for dioxin, the State may need to make a rule change to approve a site specific criteria that is based upon a different cancer slope factor. The parties also appear to disagree, at least initially, on the applicability of "footnote O" to the development of site-specific criteria. *See* Rule 750(1)(O). Nonetheless, the parties concur that if the technical teams agree to a new and different cancer slope factor as the "best available information," they will reassess the legal situation and consider appropriate action, including, a determination of the

need for a rule amendment. The assessment of non-cancer effects, though, may moot this issue if it is determined that non-cancer effects are reasonably quantifiable and are more sensitive.

Thank you again for meeting with us.

Sincerely,



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cc: Mike Robinson
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June 4, 2004

Steven Chester
Michigan Department of Environmental Quality
Constitution Hall
525 West Allegan
Lansing, MI 48913

**Re: Part 201 Criteria**

Dear Mr. Chester:

We write on behalf of Dow Chemical Company to request that, on an expedited basis, the Michigan Department of Environmental Quality (MDEQ) review and correct the current residential direct contact criterion for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin), based on the information summarized below. The materials discussed herein represent only a summary of the main issues affecting the need for a revision of the criterion.

The current dioxin criterion is inappropriate for several reasons. First, dioxin is singled out for treatment inconsistent with the equations and default assumptions adopted in the Part 201 rules for the calculation of generic direct contact criteria. Second, the dioxin criterion does not reflect the use of "only reasonable and relevant exposure pathways" as required by MCL 324.20120a(3). Third, this criterion does not use "best available information" to establish cleanup criteria, as required by MAC Rule 299.5706a(11). Moreover, Table 4 of Rule 299.5752 is inaccurate and misleading in its suggestion that no cancer slope factor is available for dioxin. MDEQ did, in fact, use a cancer slope factor in its calculation of the criterion, though the rules dictate that a lower cancer slope factor should be used in the calculation of the criterion. Additionally, certain assumptions used in the generic formula are flawed and do not reflect reasonable and relevant exposure scenarios.

Dow provided extensive comments to MDEQ during the development of the Part 201 rules, including comments on the development of a revised dioxin direct contact criterion. As a member of the Michigan Chemical Council, Dow was a Part 201 Program Advisory Group member, and in that capacity submitted comments on, among other things, proposed modifications to the Part 201 direct contact criteria formula. Dow also commented in its own

capacity on the toxicological assessment for Part 201 cleanup criteria for dioxin.[1] Those comments and MDEQ's response to them[2] discuss and acknowledge several of the necessary criterion corrections discussed herein. Additionally, Dow submitted comments on the first Part 201 rules package on September 11, 2001. That rules package did not include numerical criteria, but Dow did comment on the fact that the formulas used for the criteria development overestimated potential risks. Dow also submitted substantial comments in response to the final proposed rules package that was released on February 11, 2002. These included comments on the units used for the dioxin criteria, the ingestion rate used in the generic soil direct contact formula, the failure of the criteria to reflect the depth of the impacted soils, and the overall unreasonableness of the exposure assumptions, among other comments. In that rules package, MDEQ proposed a dioxin residential soil direct contact criteria of 150 parts per trillion (ppt), using the generic criteria formula, but failing to make adjustments previously agreed to by MDEQ.[3] The final residential soil direct contact criterion of 90 ppt adopted by MDEQ did not appear in any proposed rules package, nor in MDEQ's earlier toxicological assessment upon which Dow provided substantial comments. Dow had no opportunity to comment on the 90 ppt criterion before it was adopted as a rule.

MDEQ has justified its decision to use a different and outdated formula for calculating the dioxin criterion on the incomplete status of the draft U.S. EPA Dioxin Reassessment (Reassessment), which has been ongoing since 1991. The fact that studies concerning a compound are ongoing does not justify a departure from the standard formula for calculating direct contact criteria — after all, the same is true for virtually all compounds. Moreover, the Reassessment (1) is still in draft form and has not been actually submitted to the National Academy of Sciences, (2) has been widely and appropriately criticized, (3) is undergoing further review, and (4) makes use of flawed analyses, certain of which are discussed below. In any event, the possibility that some elements of the final Reassessment may some day affect future dioxin criterion calculations should not prevent MDEQ from currently adopting a criterion that is consistent with MDEQ's formulas for the establishment of generic criteria, and which are reflective of best available information together with reasonable and relevant exposure pathways.

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1 See Comments on Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Related Compounds, The Dow Chemical Company, October 11, 1999. A copy of this document is attached.

2 Letter, C. Flaga to A. Wallin, November 24, 1999 and enclosed Technical Response to Comments on Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Related Compounds Submitted by The Dow Chemical Company (October 11, 1999). A copy of this response is attached.

3 See discussions of dermal absorption efficiency factor and revised species scaling factor in sections II and III of this letter.

## I. The Dioxin Criterion Must Be Consistent with MDEQ's Formula for Generic Direct Contact Criteria

MDEQ's current criterion for TCDD is not based on use of the equations and default assumptions provided in the Part 201 rules for development of such criteria. Instead, the TCDD criterion is being held at values that MDEQ has used since 1998.[4] MDEQ admitted in its summary of public comments and MDEQ responses that the 1998 "dioxin criteria do not conform to the relevant rules for calculation of other cleanup criteria."[5] MDEQ also admitted that "[u]sing the up-to-date exposure factors in the rules in combination with the current toxicological inputs would result in higher criteria."[6] A copy of this response from the summary is attached. Instead of applying the up-to-date exposure factors and current toxicological inputs that have been applied as a standard, MDEQ devised a special rule for dioxin to hold the cleanup criterion at the level previously used in MDEQ guidance, stating the following:

> . . . The generic cleanup criteria for 2,3,7,8-tetrachlorodibenzo-p-dioxin are not calculated according to the algorithms presented in R 299.5714 to R 299.5726. The generic cleanup criteria are being held at the values that the department has used since August 1998, in recognition of the fact that national efforts to reassess risks posed by dioxin are not yet complete. . . .

R 299.5750(O).

MDEQ thus based its deviation from the established algorithms on the fact that a U.S. EPA review of dioxin was ongoing. At any given time, U.S. EPA is evaluating cleanup standards for any number of chemicals. If this were a valid reason for holding exposure formulas and cleanup standards at historic levels, a significant fraction of the criteria would have been held at historic cleanup levels. The simple fact that a compound is the subject of further study should not be accepted as a reason to ignore "up to date exposure factors" and "current toxicological inputs." This is particularly true when an agency has developed a revised generic formula for the calculation of cleanup criteria which it then applies to almost every other regulated compound. MDEQ's refusal to apply the generic formula to the calculation of the dioxin criteria was arbitrary and capricious. It was also in direct contravention of the statutory authority, which requires that only "reasonable and relevant exposure pathways" be considered when establishing cleanup criteria. See MCL 324.20120a(3).

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4 See Footnote R 299.5750(O).

5 See Summary of Public Comments and Department of Environmental Quality Responses Regarding Proposed Rules for Part 201, Environmental Remediation, of the Natural Resources and Environmental Protection Act, 1994 PA 453, as amended for the Public Comment Period Ending March 25, 2002, p 73.

6 Id.

As an initial correction, MDEQ should recalculate the dioxin direct contact criterion according to the algorithms presented in the Part 201 rules, to mirror the formulas used for other compounds. The majority of the changes between the 1998 formula and the Part 201 formula for residential direct contact risks reflect the fact that, overall, the 1998 formula overstated the estimated risk of exposure. There is no appropriate justification for continuing to overstate potential exposure. More specifically, the following exposure factors have changed in MDEQ's generic criteria calculations from 1998 to the passage of the Part 201 rules: (1) age-adjusted soil dermal factor, (2) skin surface area for children and adults, and (3) soil adherence factor for children and adults. In MDEQ's August 31, 1998 technical support document on generic soil direct contact criteria, the age-adjusted soil dermal factor was 2442 mg-yr/kg-day. In the Part 201 rules, that factor was changed to 353 mg-yr/kg-day. The skin surface area values for children were 1820 $cm^2$/day in 1998, compared to 2670 $cm^2$/dayevent in the Part 201 rules. For adults, the skin surface area values in 1998 were 5000 $cm^2$/day, as compared to 5800 $cm^2$/dayevent in the Part 201 rules. The soil adherence factor for both children and adults in 1998 was 1.0 mg/$cm^2$, compared to 0.2 mg/$cm^2$ for children and 0.07 mg/ $cm^2$ for adults in the Part 201 rules.

MDEQ prepared draft technical memoranda for the calculation of the direct contact criterion for dioxin in 1999 and again in 2002 using a revised formula and a revised cancer slope factor for dioxin.[7] Copies of these memoranda are attached. The formula used in those memoranda mirrors the generic direct contact formula adopted in the Part 201 rules. Using the current Part 201 formula, MDEQ calculated the generic residential direct contact criterion at 230 ppt.[8] When U.S. EPA's Dioxin Reassessment becomes finalized, U.S. EPA and MDEQ will have the opportunity to determine whether the results of the Reassessment should affect soil cleanup criteria, including the factors used to calculate the dioxin criterion under the Part 201 formula. However, deviation from the generic formula in the Part 201 rules is not justified at this time, as it unreasonably overstates potential risks associated with dioxin exposures in violation of Part 201.

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[7] See Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Related Compounds, MDEQ, May 19, 1999 and April 25, 2002.

[8] The draft Part 201 rules had proposed a residential direct contact criterion of 150 ppt. However, this was based on an outdated cancer slope factor of 75,000, which did not account for the revised species scaling factor which MDEQ was using in other programs. Use of this scaling factor results in a cancer slope factor of 45,000, which MDEQ used in the 1999 and 2002 memoranda calculating the residential direct contact criterion for dioxin at 230 ppt. See MDEQ, ERD, Part 201 Chemical Criteria Worksheet for dioxin, hand dated 4/15/02, showing calculation of 150 ppt standard based on cancer slope factor of 75,000 ("Dioxin Criteria Worksheet"). A copy of this document is enclosed.

## II. The Dioxin Criterion Must Rely on Only Reasonable and Relevant Exposure Pathways

In addition to correcting the generic formula used to calculate the dioxin criterion, certain dioxin-specific inputs into the formula should also be revised to reflect "reasonable and relevant exposure pathways" for dioxins, as required by MCL 324.20120a(3). For example the dermal absorption efficiency value used by MDEQ in the development of the generic criterion for dioxin deliberately overestimates the potential risks associated with dioxins in a manner inconsistent with MDEQ's calculation of other Part 201 criteria.

Use of upper-bound exposure assumptions for *every* factor in a criterion formula places the overall criterion outside of any actual exposure distribution, in direct conflict with Part 201's requirement that criteria must reflect only "reasonable and relevant exposure pathways."[9] In recognition of this fact, when establishing chemical-specific dermal absorption efficiencies for use in Part 201 criteria calculations, MDEQ has generally used a *central tendency* value, rather than an upper bound value. However, this method was not used for TCDD. MDEQ based its dermal absorption efficiency for TCDD of 3% on a 1992 U.S. EPA Dermal Exposure Assessment. That assessment stated that:

> The percents absorbed, corrected to reflect absorption in vivo in humans, range from 0.1% to 2.5%. The recommended percent of applied dose absorbed for TCDD is 0.1 to 3%. It is further recommended that assessors use the low end of this range for soils with high organic carbon content and the upper end for soils with low organic carbon content.

Rather than adopt a central value for TCDD that reflects typical organic carbon content soils, MDEQ adopted the upper bound value of 3%, This determination is inconsistent with MDEQ's methodology for other compounds, and it does not constitute a "reasonable exposure pathway" assumption. Therefore, the dermal absorption efficiency value for TCDD should be modified to 1.5% to reflect a central tendency value and a reasonable exposure pathway, using normal organic carbon contents in soils. In a technical response to comments submitted by The Dow Chemical Company on this issue, MDEQ discounted the low-end estimate and agreed to a midpoint value of 1.75% to calculate soil direct contact criteria.[10] This revised absorption efficiency factor at least acknowledges that a central tendency value is appropriate for this factor.

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9 See discussion of Reasonable Maximum Exposure, Part 201 Direct Contact Soil Criteria, Technical Support Document, MDEQ, ERD, January 5, 2001.

10 Letter fr C. Flaga to A. Wallin, November 24, 1999 and enclosed Technical Response to Comments on Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Related Compounds Submitted by The Dow Chemical Company (October 11, 1999). A copy of this response is attached.

The 1998 dioxin criterion currently in use does not reflect this change, and unfortunately, table 4 of Rule 299.5752 still incorporates the value of 3%. Both table 4 and the dioxin criterion should be corrected to reflect this revised dermal absorption efficiency, consistent with Part 201.

## III. The Dioxin Criterion Must Rely on Best Available Information

In the current Part 201 rules, MDEQ has designated the oral slope factor for 2,3,7,8-TCDD as "NA" or "not available." However, MDEQ has sufficient information to support calculation of an oral slope factor for 2,3,7,8-TCDD. In fact, MDEQ made use of a calculated oral slope factor to establish its 1998 criterion for 2,3,7,8-TCDD. Because MDEQ does have the ability to calculate an oral slope factor for 2,3,7,8-TCDD, it should not have identified the oral slope factor as "not available."

Even if the oral slope factor were "not available," MDEQ would be required to use "best available information" if it chose to calculate cleanup criteria for 2,3,7,8-TCDD.[11] However, the cancer slope factor used in MDEQ's calculations of cleanup criteria for 2,3,7,8-TCDD does not reflect the revised species scaling factor specifically adopted in the Part 201 rules. See MAC Rule 299.5738(5). Using different assumptions for dioxins than those used for all other substances is arbitrary and capricious, and does not constitute "best available information."

More specifically, the oral slope factor used by MDEQ to calculate the 1998 dioxin criterion was 75,000. This value was based on the Pathology Working Group's review of the original dioxin animal cancer study from Dow's Dr. Richard Kociba. MDEQ documents confirm that U.S. EPA considered this value scientifically valid.[12] This oral slope factor had assumed a species scaling factor of human body weight to the test species weight raised to the 1/3 power. However, in 1999, and again in 2002, MDEQ revisited this oral slope factor calculation, using a revised species scaling factor of human body weight to test species weight raised to the 1/4 power, consistent with U.S. EPA's proposed 1996 *Guidelines for Carcinogen Risk Assessment*, U.S. EPA's 2003 draft final *Guidelines for Carcinogen Risk Assessment,* and the administrative rules promulgated by MDEQ pursuant to Part 31 of NREPA. MDEQ adopted this revised species scaling factor in the Part 201 rules.[13] Based on currently available information, and consistent with its calculations for other substances and in other programs, MDEQ should repromulgate the Part 201 rules to formally adopt an oral slope factor of 49,000 for dioxins.

11 MAC Rule 299.5706a(11) states that if the department obtains sufficient information to support calculation of a cleanup criterion which is designated in the cleanup criteria tables or table 4 of R 299.5752 with a footnote "ID" or "NA," the department shall use best available information to calculate a cleanup criterion for the hazardous substance.

12 See Dioxin Criteria Worksheet, attached.

13 See MAC Rule 299.5738(5).

## IV. The Draft Dioxin Reassessment Does Not Constitute Best Available Information

As discussed above, the fact that development of U.S. EPA's Reassessment is ongoing does not justify deviating from using the up to date exposure factors reflected in the generic formulas for calculating cleanup criteria under Part 201. Moreover, the draft concepts appearing in the draft reassessment do not constitute "best available information," so they should not be considered in the expedited correction of the Part 201 criteria for dioxins at this time. Even U.S. EPA has not modified its proposed cleanup criteria for dioxin in response to the Reassessment.[14]

U.S. EPA's draft Dioxin Reassessment is a draft document, which is undergoing further review after substantial scientific criticism.[15] The most recent draft, from September 2000, is expressly marked "DRAFT" and includes the instruction "DO NOT CITE OR QUOTE." The draft Reassessment is not yet "available" and does not otherwise reflect "best available information." A full critique of the draft Reassessment is beyond the bounds of this letter. However, some comment is appropriate as to the draft Reassessment's use of the concept of body burden. It is our understanding that this concept is based on perceived differences in the retention and elimination of dioxins by different species (*e.g.*, the "half-life" of dioxin in rats is alleged to be much shorter than the "half-life" of dioxin in humans). While the concept of body burden may have some validity, the manner of its calculation and use in the draft reassessment is flawed.

First of all, body burden should be based on the exposure of different species under comparable conditions. In other words, estimates of the potential body burden of long-term, low dose, chronic exposures on humans should be based on the results of long-term, low dose, chronic exposure testing on other species. Unfortunately, the body burden concept as used in the draft Reassessment is based on short-term, high dose, acute exposure testing. Doses used in some of the rat studies approached levels of 50,000 times background exposure levels.

The impact of acute, single-dose exposure compared to long term exposure on responses in animal studies was examined in detail in a recent safety evaluation for dioxins conducted by

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[14] See U.S. EPA Memorandum, Approach for Addressing Dioxin in Soil at CERCLA and RCRA Sites, April 13, 1998, OSWER Directive 9200.4-26. "To date, EPA has generally selected 1 ppb as a cleanup level for dioxin in residential soils at Superfund and RCRA cleanup sites where dioxin is a principal contaminant of concern at the facility." Id. at 2. See also Record of Decision, Brunswick Wood Preserving, June 19, 2002, confirming a performance standard of 1 ppb for dioxin.

[15] Although the National Academy of Sciences (NAS) has been tasked with reviewing the draft Reassessment, it is our understanding that no current draft of the Reassessment has yet been forwarded to the NAS for review, nor has the NAS signed any formal agreement to review a draft of the Reassessment.

the European Commission Scientific Committee on Foods (ECSCF 2001).[16] In this detailed scientific review, the ECSCF relied upon studies from the U.S. EPA laboratories that demonstrated that the use of a single dose resulted in higher target tissue concentrations and greater toxic impacts than resulted from long term steady state exposures that reached the same body burden.[17] Thus, results from animal studies using single doses should not be used directly as a basis for risk assessment for ongoing, low-level human exposures.

Secondly, studies completed and published since the latest draft Reassessment confirm that the body burden assumptions relied upon in the draft Reassessment do not reflect the pharmacokinetics of dioxin exposures.[18] Most particularly, these studies show that high-dose, acute exposures to dioxin demonstrate much faster elimination in humans than was previously believed. Therefore, the use of the typical 7-year half-life in humans to extrapolate from a rat body burden to a human body burden greatly underestimates the human dose and exaggerates the theoretical risk. Error produced by the application of inappropriate half-lifes to scale from rats to humans is further compounded by the differences in rates of tissue absorption and tissue distribution that exists between a gavage study in rats and the more gradual intake of dioxins we incur from our dietary exposure.

In sum, the body burden concept as applied in the draft Reassessment does not reflect the best available information. In fact, MDEQ considered this concept, as reflected in documents drafted as recently as April 2002 (after the date of the most recent draft Reassessment) and suggested that it was inappropriate to apply this concept to the calculation of the generic dioxin criteria under Part 201 at that time.[19]

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16 European Commission Scientific Committee on Foods (ECSCF). Opinion of the Scientific Committee on Food on the risk assessment of dioxins and dioxin-like PCBs in food. Update based on new scientific information available since the adoption of the SCF opinion of 22nd November 2000. Brussels, Belgium: European Commission; May, 2001. CS/CNTM/DIOXIN/20 final.

17 The Joint World Health Organization and the United Nations Food and Agriculture Organization Expert Committee on Food Additives (JECFA) concurred with this assessment and these conclusions in their 2001 safety assessment for dioxins. Joint FAO/WHO Expert Committee on Food Additives. Fifty-seventh meeting, Rome, 5-14 June 2001, Summary and conclusions, 2001. http://www.who.int/pcs/jefca/Summary57-corr.pdf.

18 Aylward, L.L., Brunet, R.C., Carrier, G., Hays, S.M., Cushing, C.A., Needham, L.L., Patterson, D.G., Gerthoux, P.M., Brambilla, G., and Mocarelli, P. in press. Concentration-dependent TCDD elimination kinetics in humans: Toxicokinetic modeling for moderately to highly exposed adults from Seveso, Italy, and Vienna, Austria, and impact on dose estimates for the NIOSH cohort. J Expo Anal Environ Epidemiol.

19 See Draft Technical Memorandum, Calculation of Direct Contact Criteria for 2,3,7,8-tetrachlorodibenzo dioxin, MDEQ, April 25, 2002.

Another factor that has been discussed in the development of dioxin criteria is the use of a non-cancer toxicity endpoint. To the extent that a non-cancer endpoint would not incorporate the flawed body burden concept, it may be appropriate, provided that acceptable modeling techniques are employed. In fact, MDEQ's 2002 draft memo on the recalculation of the generic dioxin criteria suggested that a non-cancer endpoint might be controlling for commercial and industrial exposures. However, that memo concluded that a cancer-based criterion was controlling for residential exposures.[20]

## V. Correction of the Dioxin Criterion Should Include Correction of Generic Formula Exposure Assumptions

The correction of the dioxin criterion to reflect up to date exposure assumptions, such as those in the generic formulas, should proceed on an expedited basis, to bring the criterion into conformance with Part 201 and the other Part 201 criteria. Additionally, certain of the overall exposure assumptions used in the generic criteria formula do not reflect "reasonable and relevant exposure pathways," and so should also be corrected.

For example, in the generic direct contact criteria equations, MDEQ assumes that a person in Michigan is in contact with soils 24 hours per day, 245 days per year (excluding winter months). Although MDEQ states that its calculation of the available surface area for exposure for adults reflects climatic changes (e.g., short sleeves for 5 months and long sleeves for 3 months), MDEQ's exposed surface area value of 5,800 $cm^2$ is actually at the high end of U.S. EPA's calculation of available surface area assuming exposure of 25% of the total body surface.[21] This is essentially equivalent to wearing T-shirts and shorts for all of those 245 days. The soil contact assumptions would be both adequately protective and reasonable if MDEQ's surface area calculations actually did account for long slack and long sleeve shirt use during spring and autumn, consistent with what is identified in the U.S. EPA guidance *Dermal Exposure Assessment: Principles and Applications* (EPA/600/8-91/011B) where it states: "Assessors may want to refine estimates of surface area exposed on the basis of seasonal conditions. For example, in moderate climates, it may be reasonable to assume that 5% of the skin is exposed during the winter, 10% in the spring and fall, and 25% during the summer." MDEQ should revise its soil contact assumptions to reflect reasonable exposures based on Michigan's climate.

MDEQ also failed to use reasonable exposure pathways in establishing adult soil ingestion rates for contaminants. MDEQ currently uses an adult soil ingestion rate of 100

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20 Id.

21 The U.S. EPA Exposure Factors Handbook 1997 states: "Thus, taking 25% of the total body surface areas results in defaults for adults of 5,000 $cm^2$ to 5,800 $cm^2$, respectively."

mg/day in its residential direct contact criteria formula. This value was based on a 1991 recommendation by U.S. EPA; however, it does not reflect current U.S. EPA exposure estimates. U.S. EPA's 1997 *Exposure Factors Handbook* recommends a residential soil ingestion rate of 50 mg/day based on more recent information. Therefore, MDEQ's current value is based on an outdated recommendation that has since been replaced by the agency that made it and that fails to take account of available measurements. Continued use of the 1991 U.S. EPA value in light of its correction by U.S. EPA does not reflect a "reasonable exposure pathway." MDEQ should adopt an adult soil ingestion rate reflective of reasonable exposures.

As discussed above, it is imperative that MDEQ revise the generic soil direct contact criterion for TCDD at this time. The current formula and factors used in the calculation of that criterion are not consistent with the overall Part 201 formula, they do not reflect the best available information, they do not represent "reasonable exposure pathways," and they constitute an arbitrary and capricious misuse of MDEQ authority. Moreover, flaws in the overall generic formula are also mandated, as the current formula does not reflect reasonable exposure pathways. Therefore, the TCDD criteria must be repromulgated to be in conformance with Part 201 and the limitations on agency rulemaking authority.

Dow representatives would like to meet with you at your earliest convenience to discuss the revision of the current dioxin criterion. We will contact your office by June 11, 2004, to determine your availability for a meeting later this month.

Very truly yours,

Sharon R. Newlon

Margaret A. Coughlin
Sharon R. Newlon

MAC/eab
cc: James Sygo
Andrew Hogarth
George Bruchmann
A. Michael Leffler
Robert Reichel
Peter Wright
Bill Rustem
Jack Bails

DETROIT 25289-24 808197v02

## LIST OF ATTACHMENTS

1. Comments on Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Related Compounds, The Dow Chemical Company, October 11, 1999

2. Letter from C. Flaga to A. Wallin, November 24, 1999, including Technical Response to "Comments on Toxicological Assessment to Part 201 Cleanup Criteria for 2,3,7,8-tetrachlorodibenzo-p-dioxin and Related Compounds" Submitted by Dow Chemical Company (October 11, 1999)

3. MAC Rule 299.5750(1)(O) – Dioxin footnote for Part 201 generic criteria tables

4. Summary of Public Comments and Department of Environmental Quality (DEQ) Responses Regarding Proposed Rules for Part 201, Environmental Remediation, of the Natural Resources and Environmental Protection Act, 1994 PA 451, as amended (the Act) for the Public Comment Period Ending March 25, 2002, pp 1 & 73.

5. MDEQ ERD Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Related Compounds, L. Larsen, Ph.D., May 19, 1999

6. MDEQ ERD Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Related Compounds, TSG Dioxin Subcommittee, April 25, 2002

7. MDEQ ERD Part 201 Chemical Criteria Worksheet for 2,3,7,8-Tetrachlorodibenzo-p-dioxin {O}, hand-dated April 15, 2002

8. Part 201 Generic Soil Direct contact Criteria Technical Support Document, MDEQ ERD, January 5, 2001, pp 1-2

9. MAC Rule 299.5706a

10. MAC Rule 299.5752, Table 4, pp 141, 161-162

11. MAC Rule 299.5738

12. Approach for Addressing Dioxin in Soil at CERCLA and RCRA Sites, OSWER Directive 9200.4-26, April 13, 1998

13. EPA Superfund Record of Decision, Brunswick Wood Preserving, EPA/ROD/R04-02/027, 2002, April 19, 2002, Sec. 12.4.2

14. Opinion of the Scientific Committee on Food on the risk assessment of dioxins and dioxin-like PCBs in food. Update based on new scientific information available since the adoption of the SCF opinion of 22nd November 2000. Brussels, Belgium: European Commission; May, 2001. CS/CNTM/DIOXIN/20 final.

15. Joint FAO/WHO Expert Committee on Food Additives. Fifty-seventh meeting, Rome, 5-14 June 2001, Summary and Conclusions, 2001. http://www.who.int/pcs/jefca/Summary57-corr.pdf.

16. Abstract, Aylward, L.L., Brunet, R.C., Carrier, G., Hays, S.M., Cushing, C.A., Needham, L.L., Patterson, D.G., Gerthoux, P.M., Brambilla, G., and Mocarelli, P. in press. Concentration-dependent TCDD elimination kinetics in humans: Toxicokinetic modeling for moderately to highly exposed adults from Seveso, Italy, and Vienna, Austria, and impact on dose estimates for the NIOSH cohort. J Expo Anal Environ Epidemiol.

The Dow Chemical Company
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MICHIGAN OPERATIONS
October 11, 1999

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cc: A. Nash, Michigan Department of Environmental Quality
A. Such, Michigan Chemical Council

SUBMITTAL OF COMMENTS ON TOXICOLOGICAL ASSESSMENT AND PART 201 CLEANUP CRITERIA FOR 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN AND RELATED COMPOUNDS

Please find enclosed comments on the Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Related Compounds dated May 19, 1999. Dow Chemical appreciates the opportunity to review and comment on the document. We hope these comments will prove useful in improving the effectiveness of the criteria.

We are available to review any of these comments and provide a more in depth discussion of the issues presented. Please contact us if you are interested in a discussion of our comments.

Please let me know if you have any questions.

Anne P. Wallin

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Enclosure

# Comments on Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Related Compounds

Submitted By The Dow Chemical Company
October 11, 1999

## Executive Summary

The Dow Chemical Company (Dow) appreciates the opportunity to provide comments on the Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Related Compounds (hereafter referred to as "the Document"). Additional comments on the proposed revisions to the Part 201 Direct Contact Criteria (DCC) were submitted on July 9th and 23rd of 1999.

Dow supports and encourages many of the proposed changes that will reduce excess conservatism from the criteria while still maintaining protection for human health and the environment. However, excess conservatism still remains in the algorithms and parameters used to calculate criteria that could be adjusted and still remain protective of human health and the environment. Dow has also reviewed the toxicological studies referenced in the Document. The conclusions drawn from our review of these studies, and their application in development of the DCC, differ from those reached in the Document. The concern is that these evaluations should be as comprehensive and accurate as possible. Inaccurate conclusions can result in criteria that are overly cautious and inconsistent with the objectives and requirements of Part 201 to "remove conservatism from the standards."

Many of the submitted comments focus on the Document's conclusion that a neurobehavioral endpoint is the most sensitive non-carcinogenic endpoint, and the supporting toxicological studies. While the studies may offer valuable insight for areas warranting additional research, they are not appropriate for establishing a human neurobehavioral endpoint, nor is it scientifically sound to do so. It is important to note that even the study's authors were extremely cautious in their conclusions and indicated additional studies were needed. Liver toxicity is well established in the scientific community as the most sensitive non-carcinogenic endpoint for dioxins, and it is the appropriate endpoint to apply.

Caution is urged to provide complete, comprehensive discussions of supporting toxicological studies and issues. In some instances, the toxicological study evaluations in the Document do not discuss all the relevant aspects. For example, discussion of an immunotoxicity study referred only to the effect observed on the offspring. However, the discussion failed to mention (or reconcile) that the effect observed was immunoenhacement, not immunosuppression that is the effect most often reported for dioxin. The evaluation also did not discuss or refer to the lack of effects on the adults in the study. The "Uncertainty" section of the Document focuses on factors that might not be conservative enough, but does not address, in any manner, the health conservative nature of the assumptions made. A well-rounded and balanced discussion of each toxicological study or parameter throughout the Document will ensure an unbiased analysis.

In several cases, the criteria contain excessive conservatism either through the terms used in the algorithm, or the actual parameter value selected. Several examples to illustrate these concerns are provided.

- An adjustment factor called the "relative source contribution" has been applied to non-carcinogenic endpoints. The ultimate impact of this arbitrary factor is a five-fold reduction in the criteria for non-carcinogenic endpoints. Nominally, it is intended to account for other sources of the contaminant. However, application of the concept reveals that in actuality it appears to be a rudimentary attempt at multi-pathway risk assessment, in conflict with the intent of the Part 201 criteria. In fact, for residential soil alone, there are eleven distinct, pathway-specific criteria. The actual value for the relative source contribution term appears to have been arbitrarily derived, and its application to, and adjustment of, only non-carcinogenic endpoints lacks scientific merit.

- An adult soil ingestion rate of 100 mg/day, based on 1991 guidance for residential exposures, has been used. This rate is in conflict with the updated 1997 Exposure Factors Handbook that recommends an average adult soil ingestion rate of 50 mg/day. Use of the older number, 100 mg/day, results in the ingestion rate being an upper bound value, and incorporates yet another additional layer of conservatism into the criteria.

- The proposed criteria incorporate 245 days of dermal exposure and assume a person wears shorts and a T-shirt throughout this time. Although the current median surface areas have been used and adjusted for different ages, the combination of a high exposed surface area (shorts and T-shirt) for 9 months of the year is inconsistent with the Michigan climate. This results in the exposure being another upper bound parameter in the criteria.

- The dioxin dermal absorption efficiency parameter is based on a study that used a range of 0.1 to 2.5%. However, in development of these criteria, this parameter has been rounded up and set at an upper bound of 3%. It is imperative to note that this study overestimated an environmental exposure since it used:

    1) high contaminate concentrations (ppm levels),

    2) long exposure times (usually 48-96 h), and

    3) high soil loadings (essentially mudpacks).

    It is inappropriate to adopt the highest results in this study as the central tendency. A value of 1.5% would be more appropriate and still protective of human health and the environment.

Criteria that are unduly conservative, or cautious, ultimately hamper the effectiveness of the criteria by forcing unwarranted actions, rather than encouraging the productive and safe use of property. Unlimited use of upper bound estimates results in an estimate of exposure that will not be encountered under real world conditions. By limiting the use of upper bound estimates and addressing implicit upper bound assumptions, excess conservatism in the criteria will be reduced, and the effectiveness of the criteria will be improved while remaining protective of human health and the environment. Relying on well-established toxicological endpoints and current scientific practices for evaluating and adopting animal studies will establish a sound, scientific basis for the direct contact criteria. Many of the proposed changes are supported and are appropriate approaches. Adoption of additional suggestions will improve the overall effectiveness and scientific basis for the criteria.

## Introduction

The Dow Chemical Company (Dow) is pleased to provide comments on the Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Related Compounds (hereafter referred to as "the Document"). These comments focus on improving the effectiveness of the criteria and furthering the objective of Part 201 to "remove conservatism from the clean up standards."[1]

As reflected in comments submitted previously, the fundamental concern with DEQ's approach is the undue conservatism maintained in the Direct Contact Criteria (DCC). Several comments submitted previously (July 9 and July 23, 1999) are incorporated in the relevant sections. Criteria must be evaluated by examining all of the parameters at once. Piecemeal evaluations will ultimately lead to undue conservatism and less effective criteria.

The statutory requirement for the development of criteria was to "...appropriately characterize patterns of human exposure associated with certain land uses."[2] Consistent with this statutory requirement, EPA's guidance on exposure assessment indicates that in the overall estimation of risk or exposure, there should only be a limited number of parameters (one or two) that are at the upper end portion of their respective distributions.[3]

The technical support documents for Part 201 criteria cite this same guidance, yet most parameters have been set as upper bound (exposure frequency, exposure duration and contact rates). This practice is inconsistent with the cited guidance. In fact, application of this policy to the Direct Contact Criteria leads from 50% to almost 100% of the discretionary parameters being intentionally set at upper bound estimates. For example, within the residential DCC calculation, a total of 10 terms are used. Four of these terms are set by standard default values (slope factor, conversion factor, averaging time and the risk level), five of the remaining six discretionary parameters are clearly in the upper end of the exposure tail and the remaining term is somewhere between an average and upper bound estimate.

Default factors are already in and of themselves inherently cautious. For example, cancer slope factors are designed to reflect an upper bound estimate and not a "best" estimate. A similar situation exists for RfD's used for non-carcinogens. These are calculated to reflect an "estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a portion of the lifetime."[4]

The proposed DEQ guidance removes some undue conservatism from the Part 201 Direct Contact Criteria (DCC); however, many of the actual or implicit parameters remain upper bound estimations. Incorporating layers of conservatism leads to excessive estimation of risk that is greater than the 100% or actual risk. This practice will preclude obtaining an exposure estimate that lies within the actual distribution of exposure; which is the stated goal of EPA's exposure guidance, as well as the statutory obligation under Part 201. In order to remain consistent with EPA's exposure guidance and fulfill the statutory obligation under Part 201, fewer parameters should be set at upper bound levels; the parameters should be appropriately set at a central tendency level for the development of Direct Contact Criteria.

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[1] MDEQ 1996. The Part 201 Amendments: One Year Later.

[2] From § 324.20120a(3) of the Natural Resources and Environmental Protection Act, Act 451 of 1994, as amended.

[3] This guidance was first provided in a memorandum entitled: Guidance on Risk Characterization for Risk Managers and Risk Assessors, by Deputy Administrator F. Henry Habicht II on February 26, 1992. The intention of this memo was repeated in the EPA's Guidelines for Exposure Assessment, published in the Federal Register May 29, 1992. In March of 1995 the EPA Administrator, Carol Browner, issued a Policy of Risk Characterization that endorsed the same concepts that the estimates should be in the high end of the distribution, but plausible. The Habicht memorandum specifically identifies that only a couple sensitive parameters should be set to upper distributional values in an analysis and that the remaining numbers should be set at median or average values.

[4] Superfund Health Effects Assessment Summary Tables FY-1995, EPA/540/R-95/036, PB95-921199, May 1995, Office of Solid Waste and Emergency Response, US EPA.

Comments, which follow, are provided based on the sections of the Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Related Compounds. The appropriate header from the Document has been inserted to assist the reader. For simplicity, the word "dioxin" or "dioxins" appears repeatedly in these comments. In the context of these comments, dioxin or dioxins refers to the seventeen 2,3,7,8-substituted polychlorinated dibenzo-*p*-dioxins and dibenzofurans.

## EXECUTIVE SUMMARY (pg. 1 of the Document)

While many toxic effects have been observed in animals, their actual presence in humans remains an issue of debate. The discussion presented reads as if the research book is closed on the issue. The discussion of this area needs to be cautiously presented. It is inconsistent to conclude that clear human connections have been made, and then also conclude that human data cannot be used because of inadequate dosage information.

The conclusion that a developmental endpoint is appropriate is not supported by the science. Details for this are provided in the body of these comments.

The criteria that are proposed are more cautious than necessary to protect human health and the environment. This is partially based on the endpoints that have been selected and partially on the excessive number of conservative assumptions that have been used for the various parameters. Detailed discussions of these concerns are found in the body of the comments.

## INTRODUCTION (pg. 1 of the Document)

The description of the dioxin structure provided is confusing and potentially inaccurate, depending on the interpretation. Articles about dioxin rarely attempt to provide structural information by narrative only. If it is necessary to provide an unequivocal description of the dioxin and furan molecular structures, it is recommended that figures be used to illustrate the relevant points. If it is necessary to provide a brief description of the compounds for completeness, it is suggested that a description such as "2,3,7,8-substituted polychlorinated dibenzo-*p*-dioxins and dibenzofurans" be used. Knowledgeable scientists should be able to reconstruct the appropriate structures from such a description.

Dow agrees that the document does not address inhalation exposures and suggests the Document be renamed to more appropriately reflect the evaluations presented. The Document is not an evaluation of all cleanup criteria for dioxins. It is a Document of the toxicological and direct contact criteria evaluations for dioxins. A more accurate title could eliminate confusing references to inhalation pathways and drinking water criteria. If technical documentation is needed for other criteria, it should be addressed in a separate document and given the appropriate level of consideration and explanation. Reference to the inhalation exposure pathway should be removed to reduce confusion.

It is suggested that "preliminary findings" be removed from the Introduction section. It should be sufficient to refer to EPA's "Dioxin Reassessment" documents as "external draft review." The Document states that human studies are unreliable for regulatory purposes, however, it also attempts to draw implicit support from other selected articles of selected researchers. It would be appropriate to eliminate this last portion of the last paragraph in the Introduction and refer the reader to the EPA or ATSDR documents, as done in the next section, for a more complete discussion of research on human health effects to date. Discussion of only three articles selected from the thousands that have been published in the peer-reviewed literature may lead to an inaccurate portrayal of the information.

## TOXICOLOGICAL REVIEW (pg. 2 of the Document)

There is no comment on this portion of the Document.

### Mechanism of Action (pg. 2 of the Document)

When describing the mechanism of action for dioxin, caution is called for to avoid inappropriately extrapolating from the data. While it is true that studies indicate that dioxins bind to the Ah receptor, other compounds also bind to this receptor. Recently, it was shown that curcumin, a natural polyphenolic compound present in the spice turmeric was able to compete with 2,3,7,8-TCDD for binding to the Ah

receptor in MCF-7 cells .[5] Considering this mechanism, some toxicologists would have *de facto* considered curcumin to be a toxic compound, which would have precluded any consideration of curcumin as a therapeutic agent. Scientists at the National Cancer Institute have studied curcumin and have documented that curcumin, through one of several potential mechanisms, have a chemopreventive effect on colon cancer.[6]

While current data indicate the Ah receptor may be involved in the toxicity of dioxins, additional factors may be required. As such, expanding the standards developed here to other compounds (such as congeners), either explicitly or implicitly, simply because they bind to the Ah receptor must be approached with caution. It is appropriate to acknowledge that the mechanism has not been completely elucidated. The findings with curcumin indicate that the Ah receptor can also be associated with responses that are beneficial. Thus binding with the Ah receptor cannot be equated with toxicity, which appears to be the implications of this section. Re-writing this section to clarify what is known, and the implications, would improve the Document. An alternative would be to drop the section completely and refer the reader to other documents, such as the EPA dioxin reassessment, that can fully discuss all of the issues and ramifications.

**Carcinogenicity** (pg. 3 of the Document)

The proposed revision to the cancer slope potencies by adjusting the species body weight factor from 2/3 to 3/4 power is supported. The proposed modification is consistent with current EPA position and the position of many other governmental agencies.[7] The approach suggested adds consistency across various governmental agencies. While each agency may have a slightly different charter, the objectives often overlap. Thus, consistency in approach can lead to consistency in results, and minimize the amount of work that must be replicated by the different governmental agencies involved.

Clarification is requested regarding two specific items in this section. Specifically, the form of the model used in this analysis and the particular set of interpretations made of the Kociba slides. While the Document does reference the proposed 1996 Cancer Risk Assessment Guidelines, indicating the specific model fit would be appropriate and easy to include. Over the years, several readings have been made of the Kociba liver slides, with various slides identified as tumors under one system, but not another. Knowing which interpretation has been used would allow others to understand how the potency estimates were derived.

Consideration should be given to discussing some of the uncertainty surrounding the cancer interpretations of the Kociba study. In particular, the original interpretations of the study called into question the findings of the lung, nasal turbinates and hard palate lesions. As cited in Keenan,[8] these endpoints may have been due to contamination other than an oral ingestion. Also cited in Keenan, is an observation by several pathologists that:

> "The PWG pathologists reported a distinct correlation between the presence of overt hepatotoxicity and the development of hepatic lesions ... suggesting that the maximum tolerated dose had been exceeded in animals exposed at the higher doses."

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[5] Ciolino, H.P., Daschner, P.J., Wang, T.T.Y., and Yeh, G.C. Effect of curcumin on the aryl hydrocarbon receptor and cytochrome P450 1A1 in MCF-7 human breast carcinoma cells. *Biochemical Pharmacology* 1998, 56: 197-206.

[6] Kawamori, T., Lubet, R., Steele, V.E., Kelloff, G.J., Kaskey, R.B., Rao, C.V., and Reddy, B.S. Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer. *Cancer Research* 1999, 59: 597-601.

[7] Federal Register 24152, 57(109), 6/5/92.

[8] Keenen, R.E.; Paustenbach, D.J.; Wenning, R.J.; Parsons, A.H. (1991) Pathology Evaluation of Kociba et al. (1978) Bioassay of 2,3,7,8-TCDD: Implications for Risk Assessment. *J. Toxicol. Environ. Health*, 34: 279-296.

Based on these findings, recognition should be given that the potential for overestimating risk at low level exposures is quite likely. This is further supported by the various models and estimates that Keenan supplies in his article. Like Keenan, it is suggested that the potency estimate be based only on the cancer results observed in the liver using the most current classification for liver lesions.

**Noncarcinogenic Effects of TCDD** (pg. 3 of the Document)

For completeness in this evaluation, the discussion should indicate which endpoints were considered, but rejected, and the rationale. The current wording implies that many more endpoints were considered and a selection process applied to arrive at the specific endpoints discussed.

**Hepatotoxicity** (pg. 3 of the Document)

There is no comment on this portion of the Document.

**RfD for Hepatotoxicity** (pg. 4 of the Document)

There is no comment on this portion of the Document.

**Immunotoxicity** (pg. 4 of the Document)

The discussion of immunotoxicity is incomplete and should be expanded to better represent the studies cited. The study by Hong, et al. is mentioned as not demonstrating an adverse immunotoxic effect in low-dose offspring.[9] However, further discussion of the findings is appropriate to present a balanced picture of what is known about the immunotoxic effects of exposure. In fact, the only immunological effects observed in *any* offspring were immunoenhancement. This observation is difficult to reconcile as an effect in light of the fact that immunosuppression is the immunotoxic effect most often reported for exposure to 2378-TCDD. The significance of immunoenhancement observed, in the form of an increased response to tetanus toxoid immunization, was based on a small study size (total of seven monkeys). Only two of these monkeys had an antibody response that was clearly greater than the controls. The results observed by Hong for the offspring are interesting, but the significance of those results needs to be tempered by the size of the study, and the inconsistency of these results relative to other information. The nature of this study and its results preclude it from being an appropriate study for establishing a RfD.

The Hong paper also investigated immunological effects on the adults, and found that there were no clinically significant abnormalities in the immune response of examined adults. The study authors go further to say, "there appears to be no strict correlation between exposure levels and resulting body burden."[10] A lack of correlation would be a counter argument to the hypothesis of an immunotoxic effect. These conclusions should be included in the discussion an evaluation of the Hong study if it is included in the Document, since failure to discuss all of the study results could lead to a biased analysis.

**RfD for Immunotoxicity** (pg. 4 of the Document)

Thymic atrophy is identified as an effect with an NOAEL of 0.01 µg/kg/d, but no RfD is calculated for the effect. In light of the analysis of the Hong data discussed in the comments above, any RfD established for immunotoxicity should use the data for thymic atrophy. A NOAEL of 0.01 µg/kg/d using uncertainty factors of 10 for interspecies extrapolation and 10 to account for sensitive human individuals results in a RfD of 0.0001 µg/kg/d (or $1 \times 10^{-7}$ mg/kg/d).

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[9] Hong, R.; Tayor, K.; Abonour, R Chemosphere, 18(1-6): 313-320, 1989.
[10] *Ibid.*

**Reproductive/Developmental Toxicity (pg. 4 of the Document)**

The analysis of Reproductive and Developmental Effects should be revised to more accurately reference specific statements that accompany the studies upon which those statements are based. It is important that the discussion clarify which effects are seen at relatively high doses, particularly doses that also cause maternal toxicity, versus lower dose effects. For example, effects such as offspring mortality, cleft palate and hydronephrosis require very high doses of TCDD, which are not relevant to environmental levels.

In the current version of the Document, readers might be led to the conclusion that this long list of serious reproductive effects occurs in response to low, environmentally relevant doses of TCDD, which is not supported by the articles cited. It is critical to point out that the vast majority of reproductive and developmental studies utilized gavage dosing, in which the entire dose is administered as a bolus. This is in extreme contrast to environmental exposures that are characterized by much slower rates of exposure (i.e. exposure is in small increments over time). The pharmacokinetic differences in these two types of exposures is considerable, such that the gavage studies are not of direct relevance for human risk assessment.

Therefore, it is suggested that this list of reproductive and developmental effects is accompanied by information on the doses at which the effects were observed and the dosing method used for the study. Such information provides the appropriate context for understanding the conclusions provided in the Document and puts them in a proper and objective context. Less emphasis should be given to studies that do not reflect actual routes of exposure (such as gavage studies), and more credence given to studies that would better reflect real routes of exposure (such as feeding studies).

This section focuses on "neurobehavioral endpoints" as described in the Shantz and Bowman articles. As a result, a careful review was made of these articles and several other related articles by the cited authors.

The following comments relate specifically to the article by **Schantz, S.L. and Bowman, R.E. (1989). Learning in monkeys exposed perinatally to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).** *Neurotoxicol. Teratol.* **11: 13-19.**

As the authors remarked, the scores of the TCDD-exposed monkeys fell almost entirely within the range of control performance. Most of the learning and memory test endpoints for the reversal learning (RL) test were not statistically affected by TCDD, and none of the endpoints for the delayed spatial alternation (DSA) test were statistically significant. A positive finding was found in the group-reversal interaction term for one of the four RL tests (shape only). This was interpreted to indicate that the number of trials to criterion for one or several of the reversals was statistically different in the control group compared to the exposed group. Further examination revealed that the effect was present during the first reversal, but absent for the other seven reversals (Figure 1 of the article). Furthermore, in this instance, there were no statistically significant dose-response relationships between TCDD concentration in fat and number of trials for the first reversal in the RL test (shape). This leads to the conclusion that the majority of the learning and memory tests and data show no effects from TCDD.

One effect was reported as statistically significant (first reversal on the visual RL shape problem, $p<0.05$) because more trials were needed in the TCDD group for the first reversal than in the control group. However, the following need to be considered when interpreting these results

1. This effect was not consistent with the results of the other visual task (color).

2. When TCDD concentration was taken into consideration, no dose-response relationship was statistically significant for the RL shape problem.

3. There was a non-significant tendency towards an inverse relationship between TCDD and learning speed, as noted by the authors. Such an inverse relationship was, however, statistically significant in the RL color problem, i.e. the larger the exposure (within the context of this study), the faster the monkeys learn.

4. The cohort effect in itself ($p<0.001$) was not negligible, compared to the TCDD effect on the first reversal of the RL shape problem ($p<0.05$). In other words much of what was observed may be due simply to cohort effect and unrelated to the TCDD.

In fact, TCDD had no effect on the majority of the tested endpoints. A few statistically significant effects were reported, but in the absence of a dose-response relationship, coupled with the presence of contradictory evidence and potential confounders (cohort factor), the conclusion of an adverse effect of TCDD on learning and memory is not warranted.

Based the very large number of statistical analyses performed in this study (>70, maybe hundreds when all of the study articles are reviewed) it would be extremely surprising (statistically unlikely) to fail to record a significant p value. At an accepted error rate of 0.05, on the average 5 significant p values would be found in the absence of a true effect (i.e., false positives). The authors never discussed the problem of false positives, or the very real possibility that their findings could be due to random chance.

In light of the fact that:
- the majority of tests are negative,
- the positive effects are sometimes contradictory (e.g., motor activity),
- the positive effects are generally not dose-related, whether administered dose or concentration in fat is concerned (e.g., peer group social behavior categories),
- the learning data of the TCDD groups fall within the range of control data,
- the control data are very variable: the control data from the lead experiment (see below) are one third to about twice the control data from the TCDD experiment,
- the total number of statistical tests conducted (and p values) is very large, and
- the magnitude of the false declaration of effects (false positives) is directly proportional to the number of derived p values,

the conclusion that TCDD affects behavioral endpoints based on this article is not warranted.

There is also discussion of a companion article by **Bowman, RE, Schantz, SL, Gross, ML, and Ferguson, SA. (1989). Behavioral effects in monkeys exposed to 2,3,7,8-TCDD transmitted maternally during gestation and for four months of nursing.** ***Chemosphere*** **18: 235-242.** The following discussion is related to this article.

The authors examined a broad selection of behaviors of three groups of monkeys (control, 5-ppt and 25-ppt TCDD group). The test batteries included a very large number of endpoints, some of these not being clearly identified or defined in the paper. They also approached the study with specific bias in their interpretation *a priori*. Bowman et al. (1989) wrote in their introduction that effects caused by dioxins that appear beneficial may be the result of some adverse mechanisms and should therefore be considered as adverse. Such a position is not supported by current science nor do other scientists (NCI, FDA) broadly share this view as it could significantly impede scientific progress.

As an example of the impact of this philosophy, consider organophosphates. Organophosphates are considered by most toxicologists as causing potentially adverse effects. The literature on organophosphates has reported studies with a negative effect on memory, no effects on memory, or a positive effect on memory. The symptomatology associated with organophosphate exposure is well defined, and its mechanism of action (cholinesterase inhibition) is rather well understood. Any chemical causing cholinesterase inhibition should, therefore, be considered as potentially adverse, and it would therefore be unethical to expose humans to such chemicals on purpose. In fact, the Food and Drug Administration investigated the use of an organophosphate, metrifonate, as a therapeutic agent in Alzheimer disease to improve memory.[11] Such an action by FDA would be incompatible with the position taken by Bowman et al. (1989).

In summarizing this article, a very large number of test endpoints were normal and not statistically affected by TCDD. Some differences between control and exposed groups were recorded (statistical analysis was not always conducted to show a difference, however). The exposed monkeys appeared to be more passive than the control monkeys in the Brazelton test battery (presumably given shortly after birth). Later on, at 5.5 months of age, motor activity appeared to be increased in one exposed group, but not at any other time in that group, and not in the 25 ppt group. Less locomotion (but not dose-related) was observed around 2-4 months. These observations do not lead to a coherent picture of motor activity and, taken in context with the lack of dose-response relationship, suggest the absence of effect of TCDD on motor activity in this study.

In the mother-infant social interactions, none of the effects (but one) showed a dose-response relationship with TCDD. In the peer group social behavior, 5 out of 50 behavioral categories were identified as affected by TCDD by the authors. First, most of these effects were not straightforward, e.g. they were present on some weeks, but not other weeks in between, or a statistically significant treatment-by-gender interaction (most likely in the absence of a main treatment effect) was seen, but follow-up analyses found no differences between control and exposed groups. Second, if these effects were real, there still were no significant relationships between TCDD concentrations in fat and these effects.

Relevant to the two previous paragraphs is the lead experiment also reported in the Schantz et al. paper.[12] Attention was paid to the control observations for which data were presented, i.e. duration of mutual ventral contact (Fig. 1), duration of nipple contact (Fig. 2), and infant locomotion (Fig. 3). The performance of control group in the lead experiment was compared to the performance of the control group in the TCDD experiment at the same age (i.e., average performance over 2-4 months, p. 644). These values are given below for the two studies (the values are rough averages estimated for weeks 8-16 from Figures 1-4):

| Dependent Variable | Control (lead) | Control (TCDD) | Exposed 5 ppt | Exposed 25 ppt |
|---|---|---|---|---|
| Ventral Contact (sec/10 min) | 180 | 97 | 279 | 179 |
| Nipple Contact (sec/10 min) | 168 | 177 | 328 | 226 |
| Locomotion (sec/5 min) | 44 | 67 | 35 | 52 |

[11] Becker, R.E., Colliver, J., Elble, R., Feldman, E., Giacobini, E., Kumar, V., Markwell, S., Moriearty, P., Parks, R., Shillcut, S.D., Unni, L., Vicari, S., Womack, C., and Zec, R.F. Effects of metrifonate, a long-acting cholinesterase inhibitor, in Alzheimer disease: Report of an open trial. Drug Development Research 1990, 19: 425-434.

[12] Schantz, S.L., Laughlin, N.K., Van Valkenberg, H.C., and Bowman, R.E. (1986). Maternal care by rhesus monkeys of infant monkeys exposed to either lead or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Neurotoxicology* 7: 637-650.

In the table above, it can be seen that the control duration of ventral contact in the lead experiment was approximately double of the control duration in the TCDD experiment, and very close to the high-dose group data. The control duration of nipple contact was approximately the same in the lead experiment as in the TCDD experiment, but the duration was not dose-related. The control duration of locomotion in the lead experiment was a third lower than the control duration in the TCDD experiment, and was approximately halfway between the 5 and 25 ppt group data.

Where learning is concerned, the data tended to demonstrate the absence of a relationship with TCDD (5 times worse and 7 times better out of 12). The fact that the TCDD data fell within the range of the control data corroborated the absence of a relationship with TCDD.

As with the review of the first article, random chance would be expected to generate some statistically significant findings. In actuality the authors examined so many endpoints that the study really can only be considered a hypothesis generating analysis. It may provide insight for where additional research should be conducted, but it should not be interpreted as being definitive for regulatory purposes. In light of the same limitations cited under the review of the first article, the conclusion that TCDD affects behavioral endpoints is not warranted.

A third party outside expert's interpretation of the conclusions made in this article was sought and are included here. An effort was made to avoid bias by not identifying the authors and the chemical involved. The response received from this third party expert concluded, "... *there is not a correspondence between the monkeys in the study you cite and monkeys reared in social deprivation conditions. So, the chemical compound does not mimic the general social isolation syndrome except for self-directed behavior which may occur under many conditions including rearing with one other agemate.*"

The use of the Schantz, et al. monkey studies goes far beyond the conclusions of the study authors and is therefore not appropriate. The study authors state, "the effects observed in these TCDD studies were quite subtle and long-term follow up studies would be needed in order to determine whether the early TCDD exposure of these monkeys had any permanent effect."[13] Dow agrees that the Schantz monkey studies contain many interesting questions, or hypotheses, but the confounding factors (e.g. offspring raised by exposed mothers), constraints of the study (e.g. size of the study groups and age distributions) and exploratory nature of the statistical testing make conclusions tenuous at best. The authors point this out by saying, "In conclusion, the results of the study indicate that low level perinatal exposure to TCDD ***may*** alter the later peer group social behavior of offspring."[14] (emphasis added) Using these studies to establish a neurobehavioral development effect for humans is scientifically unsound and not warranted.

**Developmental RfD** (pg. 5 of the Document)

As indicated above, Dow does not believe that the studies cited are appropriate for setting an RfD. In addition, Dow disagrees with the manner in which DEQ calculated an RfD for developmental effects, specifically in that an additional 10x-safety factor (SF) was applied to account for sensitive human individuals (infants and children). For several reasons, Dow believes that the additional 10x SF for infants and children is not warranted in this case. First, the application of the additional SF is a very new concept which is highly controversial, with firm guidance from EPA on its application still under development. Second, the data base for TCDD on pre- and post-natal toxicity is very complete, so there is no justification for application of the additional 10x SF on the grounds of an incomplete data base. Finally, and most importantly, the RfD calculation presented in the Document is already based on a highly sensitive subpopulation (infants in the Shantz et al monkey study), but then applies an additional 10x SF for sensitive subpopulations. Given the completeness of the database and the fact that the RfD calculation is already based on the most sensitive subpopulation (infants), the weight of evidence indicates that the additional 10x SF is not needed to adequately protect infants and children.

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[13] Schantz, S.L; Ferguson, S.A.; Bowman, R.E. Neurotoxicol. Teratol., 14: 433-446, 1992

[14] *ibid.*

**BACKGROUND EXPOSURES** (pg. 5 of the Document)

It is not disputed that dioxins are present in other sources, such as food. Indeed, Dow scientists published data almost twenty years ago indicating that dioxins were ubiquitous.[15] Dow also wishes to point out that many compounds with Part 201 criteria, as diverse as benzene, acetone, ethanol and lead, are present in numerous sources encountered by people on a routine basis. However, the incorporation of the term "Relative Source Contribution," for the DCC of dioxins only, in an attempt to compensate for other sources, amounts to a rudimentary attempt at multi-pathway risk assessment. Furthermore, the distinction of using relative source contributions only for criteria with non-carcinogenic endpoints has no scientific basis and is wholly inappropriate. When an arbitrary adjustment is applied, the capricious nature of this approach and the lack of scientific merit must be recognized.

Part 201 criteria were not designed to incorporate a multi-pathway assessment of risk. Indeed that is why each compound has up to eleven distinct criteria for residential soil alone. It is worth reiterating that the algorithm for calculating criteria has already incorporated numerous cautious assumptions into the analysis, that do not require the addition of an arbitrary 20% adjustment factor, to be health protective of even highly exposed persons.

It is strongly recommended that use of the term "Relative Source Contribution" for the DCC be eliminated until such time as a better defined approach and more consistent policy is evaluated and implemented. Any use of a Relative Source Contribution term for dioxins should wait until such time as the Federal EPA has released its Dioxin reassessment and provided justification for such a term in calculating criteria.

Furthermore, if the intent is to implement a multi-pathway approach, it should proceed up-front in a straightforward manner, and the approach should be applied across all compounds with other source contributions.

**EXPOSURE ASSUMPTIONS AND CRITERIA CALCULATION** (pg. 6 of the Document)

**Exposure Values for Carcinogenic Effects (pg. 6 of the Document)**

These comments indicate general support for the parameters discussed in this section. In order to improve understanding, a brief discussion should be provided that the cancer potencies are calculated from animal studies that use relatively high doses and extrapolated to very low doses. It should also be pointed out that the potencies are based on upper bound estimates and not "best" fit calculations. This approach provides an intrinsic health protective measure to all risk assessments conducted using these potencies. Dow supports the use of exposure duration of 30 years and 21 years for residential and industrial exposures respectively. As indicated in comments submitted on July 9, 1999, duration is a parameter to be appropriately set at an upper bound since the effect on the resulting criteria is pervasive. Use of upper bound estimates for ingestion exposure frequencies of 350 days/year and 245 days/year for residential and industrial, respectively, is also supported since they directly impact multiple subsections of the model. Dow also supports DEQ's age adjusted approach for residential soil ingestion and dermal contact. However, 245 days of dermal exposure in summer attire is excessive and inconsistent with the Michigan climate.

[15] Bumb, R.R.; Crummett, W.B.; Cutie, S.S.; Gledhill, J.R.; Hummel, R.H.; Kagel, R.O.; Lamparski, L.L.; Luoma, D.L.; Nestrick, T.J.; Shadoff, L.A.; Stehl, R.H.; Woods, J.S. Science, 210: 385-390, 1980.

**Exposure Values for Developmental Effects** (pg. 6 of the Document)

While there is general agreement with the statements and case made in this section, there are two issues that need to be addressed. The primary concern is that the endpoint is inappropriate, and the second is that combination of assumptions used in the development of a DCC are excessively conservative.

With regard to an inappropriate endpoint, as discussed earlier in this document, the evidence for developmental effects in the cited studies by Shantz et al, and Bowman et al is not robust enough, nor conclusive enough to set regulatory standards. The small sample sizes used and the confounding factors present in the monkey studies make them unsuitable for developing criteria that will be viewed as definitive.

In relationship to the second matter, reference should be made to the EPA's *Guidelines for Reproductive Toxicity Risk Assessment* (EPA/630/R-96/009, September 1996). This document includes the updated philosophy of risk assessment, endorsed by the EPA, that risk estimates should lie within the distribution of actual exposures. A clear articulation of this was made in a policy memorandum in 1992 (Habicht, 1992) and reaffirmed in a risk characterization policy in 1995 (Browner, 1995). The combination of assumptions made in the Document to develop DCC values, appears to be inconsistent with this stated national philosophy.

Hepatotoxicity is a well-established, scientifically accepted non-cancer endpoint. Hepatotoxicity should be evaluated as the appropriate non-cancer endpoint, rather than an endpoint that was produced in a hypothesis generating type of experiment. It is also recommended that the combination of assumptions be scaled back to provide an estimate that does lie within the distribution of potential exposures.

**Part 201 Cleanup Direct Contact Criteria for Soils** (pg. 7 of the Document)

Within the equations supplied to calculate the DCC for noncarcinogenic developmental effects, there appear to be mathematical errors. The first error occurs on the weight used for a pregnant female; the document specifies a value of 62 kg but to arrive at the number listed 70 kg must be used. Also in comparing across the various calculations, different adherence factors are used for adults. In the calculation for a cancer endpoint DCC, a value of 0.07 $mg/cm^2$ is used while a value of 0.2 $mg/cm^2$ is used in the industrial setting. This later number matches the value used for the child in the first equation, giving the impression an error has been made. If this is not the case, then an explanation and rationale for different numbers should be provided. In addition, the adherence factors used for the non-cancer endpoint are not specified, making it difficult to verify what was done to arrive at the numbers.

Comments and concerns with the assumptions made for individual parameters are presented in a table format based on each of the various calculations made. These are presented on the following pages. More detailed discussion of these parameters was provided to DEQ in the comments submitted on July 9, 1999 and July 23, 1999.

*Table 1*
*Residential Carcinogen Parameter Summary*

| *Parameter* | *Value* | *Classification* | *Comments* |
|---|---|---|---|
| Target risk | $10^{-5}$ | Default | |
| Averaging time | 25,550 days (70 years) | Default | |
| Conversion factor | $1x10^{+9}$ µg/kg | Default | |
| Slope factor | 49,000 $(mg/kg-d)^{-1}$ | Default | As discussed earlier, DEQ should rely only on the liver lesions using the most current lesion classifications for calculating the cancer slope. |
| Ingestion exposure frequency | 350 days/year | Upper bound | Dow supports selection of an upper bound value for this parameter as *one of two* upper bound parameters. |
| Age-adjusted soil ingestion factor | 114 mg-yr./kg-day | Middle to upper bound | Please see evaluation of each distinct parameter used for calculation of this parameter. |
| Ingestion absorption efficiency | 0.5 (50%) | Upper default | |
| Dermal exposure frequency | 245 days/year | Upper bound | Dow supports selection of an upper bound value for this parameter *as one of two* upper bound parameters. |
| Age adjusted soil dermal factor | 369 mg-yr./kg-day | Upper bound | Please see evaluation of each distinct parameter used for calculation of this parameter. |
| Dermal absorption efficiency | 0.03 (3%) | Upper bound | Study range was 0.1 to 2.5%. |

*Table 2*
*Parameters Used for the Age-adjusted Soil Ingestion Factor*

| *Parameter* | *Value* | *Classification* | *Comments* |
|---|---|---|---|
| Soil ingestion rate (1-6 years of age) | 200 mg/day | High estimate of mean | |
| Exposure duration (1-6 years of age) | 6 years | Default | |
| Body weight (1-6 years of age) | 15 kg | Middle to upper | The three parameters in combination will best estimate the exposure for 1 to 3 years olds while overestimating the exposure for the remaining years. |
| Soil ingestion rate (adult) | 100 mg/day | Upper bound | Current EPA recommendation for adult mean soil ingestion rate is 50 mg/day. (1997 EPA Exposure Factors Handbook) |
| Exposure duration (adult) | 24 years | Default | |
| Body weight (adult) | 70 kg | Default | |

*Table 3*
*Parameters Used for the Age-adjusted Soil Dermal Factor*

| *Parameter* | *Value* | *Classification* | *Comments* |
|---|---|---|---|
| Surface Area (1-6 years of age) | 2,900 $cm^2$/day | Upper bound | This parameter while a mean estimate as a stand-alone piece becomes an upper bound estimate when combined with a dermal exposure frequency of 245 days. |
| Soil adherence factor (1-6 years of age) | 0.2 $mg/cm^2$ | Upper bound | While the geometric mean for "kids in mud" is higher, this would be inappropriate for 245 days per year exposure. After this the next highest geometric mean is for hands only in one set of daycare children, while the geometric mean for arms and legs in all cases, other than mud, are an order of magnitude lower. EPA Exposure Factors Handbook 1997. |
| Exposure duration (1-6 years of age) | 6 years | Default | |
| Body weight (1-6 years of age) | 15 kg | Default | |
| Surface Area (adult) | 5,700 $cm^2$ | Upper bound | This parameter, while a mean estimate as a stand-alone piece, becomes and upper bound estimate when combined with a dermal exposure frequency of 245 days. |
| Soil adherence factor (adult) | 0.07 $mg/cm^2$ | Upper bound | This value is in the upper end of the distribution for hands. While several tabled values do exceed this number for hands the geometric means for arms and legs in many cases, are one or two orders of magnitude lower. EPA Exposure Factors Handbook 1997. |
| Exposure duration (adult) | 24 years | Default | |
| Body weight (adult) | 70 kg | Default | |

*Table 4*
*Residential Non-Carcinogen Parameter Summary*

| *Parameter* | *Value* | *Classification* | *Comments* |
|---|---|---|---|
| Hazard quotient | 1 | Default | |
| Averaging time | 1 day | Default | |
| Conversion factor | $1x10^{+9}$ ug/kg | Default | |
| Oral Reference Dose | $1x10^{-9}$ mg/kg-day | Default? | An additional uncertainty factor of 10 was used to account for sensitive individuals even though the study used a very sensitive, if not the most sensitive, subpopulation- infants. |
| Body weight (adult female) | 62 kg | Median value | |
| Relative Source Contribution | 0.2 (20%) | Upper bound | This term is inappropriate and should be eliminated from the equation. It is, in essence, an arbitrary adjustment factor. |
| Exposure frequency | 1 day/year | Default | |
| Exposure Duration | 1 year | Default | |
| Soil ingestion rate | 100 mg-yr/kg-day | Upper bound | Current EPA recommendation for adult mean soil ingestion rate is 50 mg/day. (1997 EPA Exposure Factors Handbook) |
| Ingestion absorption efficiency | 0.5 (50%) | Upper default | |
| Surface area | 5,120 $cm^2$ | Upper bound | This parameter, while a mean estimate as a stand-alone piece, becomes and upper bound estimate when combined with a dermal exposure frequency of 245 days. |
| Adherence factor | 0.07 $mg/cm^2$ There is a question as to what value was used in this equation. | Upper bound | This value is in the upper end of the distribution for hands. While several tabled values do exceed this number for hands the geometric means for arms and legs in many cases, are one or two orders of magnitude lower. EPA Exposure Factors Handbook 1997. |
| Dermal absorption efficiency | 0.03 (3%) | Upper bound | Study range was 0.1 to 2.5%. |

As commented previously, the surface area used for dermal adherence should account for the climatic conditions found in Michigan. In the context of the number of days of exposure, this places the surface area as an upper bound criterion. Additionally, the current EPA recommendation for an adult soil ingestion rate of 50 mg/day should be incorporated into all criteria.

**Part 201 Drinking Water Criteria for Groundwater** (pg. 9 of the Document)

As previously discussed, it is suggested that the Document be renamed to better reflect the actual evaluations included, and this section should be deleted.

## UNCERTAINTY (pg. 10 of the Document)

In the second paragraph of this section, the clarification is needed on how the argument of "body burden" and long term average ingestion is reconciled with the procedure used for the developmental DCC calculation. This paragraph implies that the developmental DCC was based on consideration of long term dosing, which is a contradiction to the arguments provided earlier in the Document. Additional clarification should be provided.

In general, the uncertainty section addresses those factors that might not be conservative enough, but the section fails to address, in any manner, the health conservative nature of the assumptions made, either explicitly or implicitly. Neither does the section address the cumulative impact of conservative assumptions pushing estimations of exposure beyond those likely to be observed in the actual population. Failure to provide this information can provide a biased picture that some person might not be protected by the criteria, when in fact there is a very high probability that the most sensitive individual in the state will be protected with a large margin of safety based on these calculations. There should be a very open discussion of both the pros and cons of particular parameter selections, and all of the limitations associated with those choices.

## TOXIC EQUIVALENCY FACTORS (pg. 11 of the Document)

Additional discussion of a few aspects of the Toxic Equivalency Factors approach for estimating the risk of dioxin and furan mixtures is appropriate for completeness. The numerous studies cited for establishing the potency, carcinogenic and non-carcinogenic effects, discussed thus far in the Document all used 2,3,7,8-tetrachlorodibenzo-*p*-dioxin exclusively. This has been the typical practice to simplify the study protocol and interpretations. It also makes comparisons between studies easier by removing a variable. However, the Toxic Equivalency Factors approach has uncertainty and limitations associated with it, as stated in the report.[16] Readers who are not experts in the area of dioxin toxicology might assume that each "TEF isomer" has convincing in vivo data to establish its TEF. Clearly this is not the case, and the report provides explicit discussion of the procedure's limitations. In addition, studies have been conducted which evaluate the methods used to derive the Toxic Equivalency Factors, and the degree of toxicity overestimation that is incorporated into the approach.[17]

In the second to the last sentence of the first paragraph under Toxic Equivalency Factors, an argument is presented concerning Ah receptor binding to support the use of TEFs in toxicity evaluations. It should be noted that TEF's are based on the assumption that toxicity of TCDD-related molecules involves a common mechanism of action based on the Ah receptor. However, there are few data definitively linking reproductive effects with Ah receptor activation. Thus, applying a TEF to reproductive effects would seem to lack a strong scientific grounding. As was pointed out earlier in these comments compounds, such as curcumin, have been demonstrated to bind to the Ah receptor, BUT provide a protective effect, NOT a toxicological effect.

It is not necessary to abandon Toxic Equivalency Factors for Part 201 criteria. However, it is appropriate to discuss the cautious nature of the approach. The TEFs may represent actual toxicity, but evidence to date would suggest that they probably overestimate the actual toxicity of the combined congener exposure. Thus, the use of TEFs is a sound rationale for not requiring additional conservatism in other parameters, such as use of the relative source contribution term and the additional RfD uncertainty factors.

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[16] U.S. Environmental Protection Agency, Interim Procedures for Estimating Risks Associated with Exposures o Mixtures of Chlorinated Dibenzo-*p*-dioxins and Dibenzofurans (CDDs and CDFs) and 1989 Update, EPA/625/3-99/016, 1989.

[17] Kociba, R.J. Solving Hazardous Waste Problems Learning from Dioxins, J.H. Exner, ed., ACS Symposium Series 338, Washington DC, 1987, p 54-67. Suter-Hofmann, M.; Schattler, Ch. Chemosphere, 15(9-12): 1733-1743, 1986. Janz, D.M.; Metcalfe, C.D. Chemosphere, 23(4): 467-472, 1991.

## Appendix A

**Formal review of Schantz, S.L. and Bowman, R.E. article**
**Learning In Monkeys Exposed Perinatally To 2,3,7,8-Tetrachlorodibenzo-P-Dioxin (TCDD)**

**in**

*Neurotoxicology and Teratology*
**(11: 13-19)**

**by**

**Jacques P. Maurissen, Ph.D.**

Ten control and 10 TCDD-exposed (5 ppt in diet) rhesus monkeys (7 control and 5 exposed from cohort I, and 3 control and 5 exposed from cohort II) were tested for learning and memory on discrimination-reversal learning (RL) and on delayed spatial alternation (DSA). The RL test was subdivided into 4 components: spatial-1, spatial-2 (with irrelevant cues), visual-color, visual-shape.

The learning and memory effects on can be summarized as follows:

- There were no significant group main effects ($p>0.05$) on offspring in:
  - the shaping procedures which preceded the RL test
  - the shaping procedures which preceded the DSA test
  - overtraining for the trials to criterion in the RL test – spatial-1
  - overtraining for the trials to criterion in the RL test – spatial-2
  - overtraining for the trials to criterion in the RL test – color
  - overtraining for the trials to criterion in the RL test – shape
  - the trials to criterion in the RL test – spatial-1
  - the trials to criterion in the RL test – spatial-2
  - the trials to criterion in the RL test – color
  - the trials to criterion in the RL test – shape
  - percent correct performance on the DSA test
  - latency on the DSA test
- There were significant effects of TCDD ($p<0.05$) on offspring in:
  - TCDD by reversal interaction in the RL test – shape
  - post hoc test: first reversal in the RL test – shape (but no correlation between TCDD in body fat and trials to criterion for first reversal on RL test shape)
  - cohorts for percent correct performance on the DSA test (irrespective of treatment)

In summary, most of learning and memory test endpoints for the RL test were not statistically affected by TCDD, and none of the endpoints for the DSA test were statistically significant. A positive finding was found in the group x reversal interaction term of the analysis of variance (ANOVA) for one of the 4 RL tests (shape only), indicating that the number of trials to criterion for one or several of the reversals was statistically different in the control group compared to the exposed group. Further analysis revealed that the effect was present during the first reversal, but absent for the other 7 reversals (Figure 1). Furthermore, in this instance, there were no statistically significant dose-response relationship between TCDD concentration in fat and number of trials for the first reversal in the RL test (shape). As the authors also remarked, the scores of the TCDD-exposed monkeys fell almost entirely within the range of control performance.

It should also be made clear that:

1. A statistically significant effect was seen on visual, but not on spatial performance of the RL test. In light of the lack of a consistent effect on learning, it has been argued that an effect on one type of RL test (e.g., visual: shape and color components) would not necessarily imply an effect on another type of RL test (e.g., spatial: spatial-1 and spatial-2 components). However, if TCDD adversely affects the visual component of the RL test, it should also affect the color (i.e., visual) component (besides the shape component), which is not the case as reflected by the absence of a main group effect on color problems. As a matter of fact, examination of Figure 2 shows that there is an inverse relationship between TCDD in body fat and trials to criterion at first reversal of the RL test (color), which means that monkeys with high concentrations of TCDD took less trials to learn the first reversal, i.e. learned faster (within the context of this study). This inverse relationship is declared statistically significant by the authors (p. 16).
2. Also mentioned above, there was a statistically significant difference between cohorts in the DSA test, irrespective of treatment. In other words, when performance of cohort I (control and treated together) was compared to performance of cohort II (control and treated together), there was a main effect of cohort ($p<0.001$), i.e. the differences between two separate samples of animals were statistically significant, irrespective of treatment. This shows that pre-existing differences between groups could be confounded with a treatment effect.

Conclusion: the majority of the learning and memory tests and data show no effects of TCDD. One effect was reported as statistically significant (first reversal on the visual RL shape problem; $p<0.05$): more trials needed in the TCDD group for the first reversal than in the control group. This effect was not consistent with the results of the other visual task (color). Furthermore, when TCDD concentration was taken into consideration, no dose-response relationship was statistically significant for the RL shape problem, and examination of these data showed that there was a nonsignificant tendency towards an inverse relationship between TCDD and learning speed, as noticed by the authors. Such an inverse relationship was, however, statistically significant in the RL color problem, i.e. the larger the exposure (within the context of this study), the faster the monkeys learn. Finally, the cohort effect in itself ($p<0.001$) was not negligible, compared to the TCDD effect on the first reversal of the RL shape problem ($p<0.05$). TCDD had no effect on the majority of the tested endpoints. A few statistically significant effects were reported, but in the presence of a lack of dose-response relationship, contradictory evidence and potential confound (cohort factor), the conclusion of an adverse effect of TCDD on learning and memory is not warranted.

## Appendix B

## Formal review of the Bowman, RE, Schantz, SL, Gross, ML, and Ferguson, SA. article Behavioral Effects In Monkeys Exposed To 2,3,7,8-TCDD Transmitted Maternally During Gestation And For Four Months Of Nursing

in

*Chemosphere*
(18: 235-242)

by

Jacques P. Maurissen, Ph.D.

The authors examined a broad selection of behaviors of 3 groups of monkeys (control, 5-ppt and 25-ppt TCDD group). The test batteries included a very large number of endpoints, some of these not being clearly identified or defined in the paper. However, a summary of the results is presented below. No differences between control and treated groups were seen in:

- birth weight
- growth
- fine motor control
- Hamilton search task (cognitive test)
- Hypothalamus-pituitary-adrenal axis endocrine tests, such as:
  - response to adrenocorticotrophic hormone (ACTH) infusion
  - dexamethasone suppression
- most items of the Brazelton-type neonatal behavioral assessment test battery which encompass the following test domains:
  - sensory responsivity
  - neuromotor development
  - temperament
- Piagetian concept formation (cognitive test)
- overall percent correct performance on the DSA (cognitive test): "Sequential trial" analysis showed no effects at two years of age, but at 6 years of age, the "% correct responses of the 5 ppt group on trial n was correlated with that on trial n-1, but not on trial n-2". The biological significance of such a "pattern" is far from being clear, the authors themselves did not comment about it and ignored it in their abstract and discussion.
- The article by Schantz et al. (1986), referenced in this paper, complements this paper and shows that the TCDD infant monkeys (2-4 months of age) had no differences in:
  - body weight
  - physical appearance
  - health
  - social behavioral pattern:
    - groom
    - social explore
    - approach
    - reject/withdraw
    - hostility
    - orient
    - vocalization
  - nonsocial behaviors:
    - play
    - hang
    - stereotypy
    - eating/drinking

Differences between control and treated groups were seen in:

- passivity (from Brazelton-type test battery): TCDD monkeys are more passive
- increased locomotor activity "in the 5 ppt group of Cohort I tested at 5.5 months of age, but "No locomotor effects were seen in them at any other time, nor at any time on any other of the groups" (Bowman et al., 1989, p. 238)

- mother-infant social interactions. No data are given in this paper, but the article by Schantz et al. (1986) is referenced and shows that the TCDD infant monkeys (2-4 months of age) had significantly ($p<0.05$):
  - more time in ventral contact with mother (not dose-response related; Fig. 4A).
  - more time in nipple contact with mother (not dose-response related; Fig. 4B).
  - less locomotion (not dose-response related; Fig. 4C). The effect went away when locomotion was analyzed as a proportion of total time spent away from mother.
  - been approached more by the mothers (in a dose-response related manner; Fig. 5A)
  - approached the mothers less frequently (not dose-response related; Fig. 5B)
  - mutually broken contact with the mothers (not dose-response related; Fig. 5C)
- peer group social behavior: Out of 50 behavioral categories, the following ones were reported as significantly affected by TCDD [if tested in mixed groups for cohort I (which was born 16 months after TCDD maternal exposure), but only if tested in unmixed groups for cohort III (which was born 18 months after maternal TCDD exposure)]:
  - "initiate" rough tumble play (Fig. 2 in Schantz and Bowman, 1989; same data also published in Fig. 2 of Schantz et al., 1992): significant differences on weeks 5, 8 and 9 of testing. There were no significant differences for the "receive" or "mutual" rough-tumble play categories. Overall, there were no significant differences between control and TCDD in the single category rough-tumble play (Schantz et al., 1992, p. 437).
  - play retreat
  - yield to displacement: the TCDD-exposed monkeys were less often displaced from positions than were control monkeys.
  - self-directed behaviors: the TCDD-exposed monkeys were engaged in more self-directed behaviors. Both control and TCDD females also engaged in more self-directed behavior than control and TCDD males (Schantz et al., 1992, p. 437).
  - environmental exploration: a statistically significant "treatment by gender interaction" was found, but follow-up tests (Schantz et al., 1992, p. 437) did show no differences between:
    - TCDD males and TCDD females
    - control males vs. TCDD males
    - control females vs. TCDD females

  Furthermore, there were no significant relationships between TCDD concentrations in body fat and the above behavioral effects (Schantz et al., 1992, p. 437-438).
- First reversal (out of 8) of the discrimination reversal learning (DRL) (cognitive test) at about 4 months of age. Data from Fig. 8 show that the required number of trials to reach some defined criterion tend to increase (5 times out of 12) or decrease (7 times out of 12) within treatment groups when the TCDD concentration in fat increases, i.e. speed of learning in 4 different learning tasks increases more often that it decreases when TCDD increases. The authors also remark that the percent correct data (i.e., measure of learning) associated with the TCDD groups fall within the range of the percent correct data of the control group.
- Visual exploration (marginally significant, i.e., $p<0.1$ most likely)

In summary, a very large number of test endpoints were normal and not statistically affected by TCDD. Some differences between control and exposed groups were recorded (statistical analysis was not always conducted to show a difference, however). The exposed monkeys appeared to be more passive than the control monkeys in the Brazelton test battery (presumably given shortly after birth). Later on, at 5.5 months of age, motor activity appeared to be increased in one exposed group, but not at any other time in that group, and not in the 25 ppt group. Less locomotion (but not dose-related) was observed around 2-4 months. These observations do not lead to a coherent picture of motor activity and, taken in context with the lack of dose-response relationship, suggest the absence of effect of TCDD on motor activity in this study.

In the mother-infant social interactions, none of the effects (but one) showed a dose-response relationship with TCDD. In the peer group social behavior, 5 out of 50 behavioral categories were identified by the authors as affected by TCDD. First, most of these effects were not straightforward, e.g. they were present on some weeks, but not on some other weeks in between, or a statistically significant treatment-by-gender interaction (most likely in the absence of a main treatment effect) was seen, but follow-up analyses found no differences between control and exposed groups. Second, if these effects were real, there still were no significant relationships between TCDD concentrations in fat and these effects.

Relevant to the two previous paragraphs, is the Pb experiment also reported in the Schantz et al. (1986) paper. Attention was paid to the control observations for which data were presented, i.e. duration of mutual ventral contact (Fig. 1), duration of nipple contact (Fig. 2), and infant locomotion (Fig. 3). The performance of control group in the Pb experiment was compared to the performance of the control group in the TCDD experiment at the same age (i.e., average performance over 2-4 months, p. 644). These values are given below for the two studies (the values are rough averages estimated for weeks 8-16 from Figures 1-4):

| Dependent Variable | Control (Pb) | Control (TCDD) | Exposed 5 ppt | Exposed 25 ppt |
|---|---|---|---|---|
| Ventral Contact (sec/10 min) | 180 | 97 | 279 | 179 |
| Nipple Contact (sec/10 min) | 168 | 177 | 328 | 226 |
| Locomotion (sec/5 min) | 44 | 67 | 35 | 52 |

In the table above, it can be seen that the control duration of ventral contact in the Pb experiment was approximately double of the control duration in the TCDD experiment, and very close to the high-dose group data. The control duration of nipple contact was approximately the same in the Pb experiment as in the TCDD experiment, but the duration was not dose-related. The control duration of locomotion in the Pb experiment was a third lower than the control duration in the TCDD experiment, and was approximately halfway between the 5 and 25 ppt group data.

As far as learning is concerned, the data tended to demonstrate the absence of a relationship with TCDD (5 times worse and 7 times better out of 12). The fact that the TCDD data fell within the range of the control data corroborated the absence of a relationship with TCDD.

Conclusion: Taking into consideration the very large number of statistical analyses that were performed in this study (>70, maybe hundreds) or in any study for that matter, it would be extremely surprising (statistically unlikely) to record no significant p value. At an accepted error rate of 0.05, on the average 5 significant p values would be found in the absence of a true effect (i.e., false positives). The authors never discussed the problem of false positives.

In light of the fact that
- the majority of tests are negative,
- the positive effects are sometimes contradictory (e.g., motor activity),
- the positive effects are most of the times not dose-related, whether administered dose or concentration in fat is concerned (e.g., peer group social behavior categories),
- the learning data of the TCDD groups fall within the range of control data,
- the control data are very variable: the control data from the Pb experiment are one third to about twice the control data from the TCDD experiment,
- the total number of tests (and p values) is very large,
- the magnitude of the false declaration of effects (false positives) is directly proportional to the number of derived p values,

the conclusion that TCDD affects behavioral endpoints is not warranted.

## Appendix C

## References for Reviews in Appendices A and B

Bowman, R.E., Schantz, S.L, Gross, M.L., and Ferguson, S.A. Behavioral effects in monkeys exposed to 2,3,7,8-TCDD transmitted maternally during gestation and for four months of nursing. *Chemosphere* 1989, 18, 235-242.

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Ciolino, H.P., Daschner, P.J., Wang, T.T.Y., and Yeh, G.C. Effect of curcumin on the aryl hydrocarbon receptor and cytochrome P450 1A1 in MCF-7 human breast carcinoma cells. Biochemical Pharmacology 1998, 56, 197-206.

Kawamori, T., Lubet, R., Steele, V.E., Kelloff, G.J., Kaskey, R.B., Rao, C.V., and Reddy, B.S. Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer. *Cancer Research* 1999, 59, 597-601.

STATE OF MICHIGAN

JOHN ENGLER, Governor

DEPARTMENT OF ENVIRONMENTAL QUALITY

*"Better Service for a Better Environment"*

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RUSSELL J. HARDING, Director

REPLY TO:

ENVIRONMENTAL RESPONSE DIVISION
KNAPPS CENTRE
PO BOX 30426
LANSING MI 48909-7926

November 24, 1999



Anne P. Wallin, Ph.D.
The Dow Chemical Company
Environmental, Health & Safety
1261 Building
Midland, MI 48667

Dear Dr. Wallin:

Thank you for your October 11 comments on the Toxicological Assessment and Part 201 Cleanup Criteria for Dioxins. This letter represents the Environmental Response Divisions's (ERD's) response to those comments. The technical details and discussions related to the toxicity assessment are presented in the attached document, however, a few general comments are made here.

Although most of the comments in this cover letter pertain to the executive summary, we have one comment related to the introduction. The statement is made in the introduction that "...the objective of Part 201 is to remove conservatism from the cleanup standards." This is an incorrect representation of the 1995 amendments (and possibly a typographical error); the intent of the Part 201 amendments was never to remove all conservatism from the cleanup standards. **One** of the objectives of the Part 201 **amendments** was to remove **excess** conservatism from the cleanup standards. To fulfill the purpose of allowing unrestricted, safe use (both current and future) of contaminated property, the generic cleanup criteria algorithms must be appropriately conservative to address a wide range of activities and individuals with wide-ranging sensitivities and behavioral patterns. The other objectives of the 1995 amendments were to put fairness in the liability scheme and provide assistance in returning brownfield property to productive use.

The remaining comments pertain to the executive summary:

1) The comment is made in Dow's executive summary that "a well-rounded and balanced discussion of each toxicological study or parameter...will ensure an unbiased analysis." When comprehensive summaries of the toxicity database for a hazardous substance are available in a document written by a federal agency such as the Agency for Toxic Substances and Disease Registry (ATSDR) or the United States Environmental Protection Agency (EPA), it is the Toxicology Unit's standard practice to use and refer to those documents rather than conduct an intensive review of the literature. Such a practice exists for the sake of efficiency and is necessary due to limited staffing resources. We typically review the summary document and identify the best and most pertinent studies and focus on those for our written assessment. We use our best professional judgement to identify the best studies and discuss the most pertinent aspects of the selected studies.

2) Dow's executive summary also states that the Part 201 criteria are unduly conservative and upper bound estimates of exposure are used without limitation. The generic exposure

assumptions used to generate the Part 201 cleanup criteria are established following the EPA Risk Assessment Guidance for Superfund (RAGS). The EPA recommends using upper end estimates of the mean for the most sensitive parameters (typically contact rates, exposure duration and exposure frequency) and central tendency estimates for the remaining parameters. For the purpose of estimating a reasonable maximum exposure rather than a worst case exposure, the EPA recommends "*identifying the most sensitive parameters in the risk assessment and using maximum or near-maximum values for one or a few of these variables, leaving others at their mean values. When the principal parameters of the dose equation (e.g., concentration, intake rate, duration) are broken out into subcomponents, it may be necessary to use maximum values for more than two of these subcomponent parameters, depending on a sensitivity analysis.*"[1] A table has been prepared and is presented in the attached document which identifies whether an exposure parameter is represented by an upper percentile or central tendency estimate of the mean. Examination of this table will demonstrate that EPA guidance has been followed. Application of EPA's guidance results in development of criteria which are reasonably but not overly conservative. This process allows for unrestricted current and future use which is the purpose of the generic residential criteria. The question is being asked on both the federal and state level: are current regulations protective of children? Until this question is answered, attempts to make the criteria less conservative, particularly when inconsistent with EPA guidance, should be considered with caution.

3) The generic issues related to the dermal portion of the direct contact equation (i.e., skin surface area and the related exposure frequency) will be decided by Deputy Director Arthur Nash Jr. ERD has determined that these factors have little affect on the cleanup criteria values. As such ERD has taken a simple approach to calculating the skin surface area for children and adults by assuming that the area available for dermal contact with soil will not vary throughout the assumed 245 day per year exposure frequency. ERD agrees that a more rigorous approach that considers seasonal weather conditions in Michigan would indicate that less skin surface area is available during the colder spring and fall months. However, more skin surface area would be available during the warmer months than is currently assumed using ERD's simple approach. A rigorous and time consuming calculation that considers the varying weather conditions in Michigan is not likely to yield a skin surface area significantly different from that currently used by ERD. In addition, ERD's current simple approach gives greater weight to dermal exposure of children to soil contaminants. Dow's suggested adjustment to the skin surface area would result in criteria that are less protective of children.

4) Dow made the comment that application of the relative source contribution (RSC) factor is a rudimentary attempt at multipathway risk assessment. A multipathway risk assessment on a contaminated property would evaluate the combined risks from all exposures occurring at the site. The generic Part 201 soil direct contact criteria (DCC) for TCDD account only for incidental ingestion of and dermal contact with soil. Other pathways of exposure that could be present at a site of environmental contamination are not considered and are not accounted for by the application of the RSC. In general, the RSC attempts to account for exposures to hazardous substances from sources other than the site. The EPA Office of Drinking Water uses the RSC factor in development of drinking

[1] F. Henry Habicht II, Deputy Administrator of the EPA. Guidance on Risk Characterization for Risk Managers and Risk Assessors. February 26, 1992.

water standards to account for other exposures to the same chemical received from food and air. Ignoring exposures from sources other than the site, particularly for those hazardous substances where such exposure may be significant, could result in adverse health effects. Part 201, Environmental Remediation, of the Natural Resources and Environmental Protection Act, 1994 PA 451, as amended (NREPA) states: "For the noncarcinogenic effects of a hazardous substance present in soils, the intake shall be assumed to be 100 percent of the protective level, unless compound and site-specific data are available to demonstrate that a different source contribution is appropriate." The statute allows for the use of chemical and site-specific information to adjust the default RSC factor of 100 percent. Although the background concentrations of dioxins in food come from national food basket surveys, it is expected that concentrations of dioxins in Michigan's food supply is similar. More specific information related to dioxins in food is presented in the attached document.

We look forward to discussing these issues with you at the meeting scheduled on December 6, 1999, at 10:00 a.m., held in the Great Lakes Conference Room on the 6th Floor of the Hollister Building. We hope that submitting this response to you prior to the meeting will facilitate a productive and efficient meeting. If you have questions, please call me.

Sincerely,

Linda D. Larsen for

Christine Flaga
Toxicology Unit
Environmental Response Division
517-373-0160

Attachments

cc: Mr. Arthur R. Nash Jr., MDEQ
Mr. Alan J. Howard, MDEQ
Mr. Andrew W. Hogarth, MDEQ
Dr. Linda Larsen, MDEQ
Mr. Jeffrey Crum, MDEQ

**TECHNICAL RESPONSE**
to
"Comments on Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-tetrachloro-*p*-dioxin and Related Compounds"
Submitted by The Dow Chemical Company (October 11, 1999)

**The Environmental Response Division (ERD) responses to comments contained in Dow's Executive Summary**

**Dow Comment:** Dow indicates that the dermal absorption efficiency ($AE_d$) of 3.0% used to develop the soil direct contact criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) represents an upper bound value of the reported range of 0.1 to 2.5 percent. Further, Dow states that the study which reports these values used (1) high contaminant concentrations (part per million or ppm levels), (2) long exposure times (usually 48-96 hours), and (3) high soil loadings (essentially mudpacks).

**Response:** The ERD has obtained the original study[1] that serves as the basis for the United States Environmental Protection Agency (EPA) recommended $AE_d$ of 3.0 percent. This information was not available in May. The contaminant concentration of TCDD used in both *in vivo* and *in vitro* trials was one part per million. While observations were made over a span of 96 hours, the recommended $AE_d$ values represent dermal absorption at 24 hours. Data obtained after 96 hours were used only to describe the relationship between *in vivo* and *in vitro* animal results and between animal and human *in vitro* results. The soil loadings of 10 $mg/cm^2$ are higher than would be expected under normal conditions of exposure and, therefore, the *total* dose of TCDD applied to the dermal surface would be higher than expected under normal exposure. However, the absorbed dose expressed as a fraction or percentage of the total applied dose is not expected to vary significantly based on soil loading.[2]

The lowest value of 0.1 percent for the reported range of $AE_d$ was observed following dermal application of TCDD in soil containing a fraction of organic carbon ($f_{oc}$) of 11.2 percent. Except for sediments or highly organic soils in wetland areas, soils in Michigan generally exhibit $f_{oc}$ values of 0.1 to 1.3 percent. Therefore the $AE_d$ observed for soils with 11.2 percent organic carbon is inappropriate for the development of generic Part 201 criteria.

Adjusted human $AE_d$ values for TCDD reported for soils with an $f_{oc}$ of 0.45 percent (consistent with soils in Michigan) are 0.95 and 2.5 percent. These values were calculated from mean percents absorbed for four or five test animals or excised skin samples and, therefore, represent average values. Human *in vitro* data from excised skin samples were adjusted using the ratio of animal *in vivo*/animal *in vitro* to derive the estimated human *in vivo* value of 0.95 percent. Animal *in vivo* data were adjusted using the ratio of human *in vitro*/animal *in vitro* to derive the estimated human *in vivo* value of 2.5 percent. Both approaches are equally valid and provide estimates of average human dermal absorption efficiency for TCDD. Therefore, the ERD suggests a midpoint value of 1.75 to calculate soil direct contact criteria.

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[1] EPA (U.S. Environmental Protection Agency). 1991. Percutaneous Absorption of 2,3,7,8-Tetrachlorodibenzo-p-dioxin and 3,3',4,4'-Tetrachlorobiphenyl Applied in Soil (Review Draft). OHEA-E-453.

[2] EPA (U.S. Environmental Protection Agency). 1992. Dermal Exposure Assessment: Principles and Application. Office of Health and Environmental Assessment. EPA/600/6-88/005Cc.

The above discussion and revision to the TCDD criteria and any others indicated in the following responses will be included in a revised Toxicological Assessment (TA) for TCDD. A revised TA is not available at this time, but will be provided to Dow when completed.

Additional comments contained in the Executive Summary of Dow's submittal are addressed by the ERD in the toxicological review section below and in the attached cover letter.

**The ERD responses to comments contained in Dow's Introduction**

Comments contained in the Introduction of Dow's submittal are addressed by the ERD in the toxicological review section below and in the attached cover letter.

**The ERD responses to Dow comments on the ERD Toxicological Assessment (TA) for TCDD** (Headings refer to sections of the TA.)

EXECUTIVE SUMMARY

Dow's comments on the EXECUTIVE SUMMARY are addressed by the ERD in the toxicological review section below and in the attached cover letter.

INTRODUCTION

**Dow Comment:** Dow comments on the narrative description given for the physical structure of dioxin-like compounds and suggests the inclusion of a figure.

**Response:** The narrative language that describes the physical structure of dioxin-like compounds is similar to that given in Chapter 3 of the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Chlorinated Dibenzo(p)Dioxins (1998). The ERD Toxicological Assessments (TAs), like the ATSDR profiles, are written in language intended to be understood by a person with no advanced training in toxicology (i.e., the "educated layperson"). While this may lead to some loss of precision in technical descriptions, it is presumed that knowledgeable scientists will have little difficulty understanding concepts written in this fashion. The ERD agrees to incorporate an illustrative figure in this section to lessen any potential confusion as to the physical structure of the dioxin-like compounds considered in the assessment.

**Dow Comment:** Dow suggests a change in the title for the Toxicological Assessment (TA).

**Response:** The ERD agrees to change the title to the following: TOXICOLOGICAL ASSESSMENT AND PART 201 SOIL DIRECT CONTACT CLEANUP CRITERIA FOR 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN AND RELATED COMPOUNDS. An introductory paragraph will also be added before the Executive Summary indicating which pathways and routes of exposure will be considered in the TA.

TOXICOLOGICAL REVIEW

**Dow Comment:** Dow comments that other compounds such as curcumin also bind to the Ah receptor and that some toxicologists would consider this compound to be toxic based on its binding affinity to the Ah receptor.

**Response:** Dioxin-like compounds are thought to be Ah receptor agonists. Simply stated, agonistic compounds bind to a receptor and produce a response. By contrast curcumin is considered to be an Ah antagonist. Antagonistic compounds compete for binding to a receptor site, but block rather than produce a response. It is unlikely that a toxicologist would determine

a compound to be toxic based on its affinity for a receptor without consideration of the resulting effect.

The ERD agrees to add language to this section indicating that the role of the Ah receptor and the responses it mediates have not been clearly defined for dioxin and related compounds. However, this section is important as a basis for understanding the Toxic Equivalency Factor (TEF) approach discussed later in the TA and, therefore, will be retained.

CARCINOGENICITY

**Dow Comment:** Dow requests clarification of the model and data used to develop the oral cancer slope factor.

**Response:** The ERD oral cancer slope factor (SF) for TCDD is calculated based on the total number of tumor bearing animals from Kociba, et al., (1978) using the 1990 Pathology Working Group (PWG) liver analysis. The TA clearly states that the PWG 1990 re-analysis of liver slides was used to calculate the SF. The ERD uses the linear multistage (LMS) cancer model (as calculated using Global 82) for all cancer assessments unless the EPA has determined an alternate model is more suited to the chemical-specific data. The EPA may recommend an alternate model for TCDD when the final Dioxin Reassessment is published. In the interim, the ERD judged the LMS cancer model to be sufficient and protective of public health.

NONCARCINOGENIC EFFECTS OF TCDD

**Dow Comment:** Dow requests that the ERD indicate which noncarcinogenic endpoints were considered but rejected and the rationale for selecting which endpoints to consider.

**Response:** The analyses in ATSDR (1998) and the EPA (1994) were relied upon to focus the ERD assessment to the three noncarcinogenic endpoints considered to be most critical for TCDD: immunotoxicity, developmental and reproductive toxicity, and hepatotoxicity. The ERD does not have the necessary resources to conduct a *de novo* review of the thousands of toxicological studies on TCDD in the available literature and must rely upon federal agencies whenever possible. As indicated on page 2 of the TA, the reader is referred to ATSDR (1998) and EPA (1994) for additional information. In addition, the World Health Organization (WHO) has identified developmental/reproductive, immunotoxicity, and hormonal effects to be sensitive non-cancer effects for TCDD in animals.[3]

IMMUNOTOXICITY

**Dow Comment:** Dow requests expansion of the discussion of immunotoxicity.

**Response:** The ERD will provide additional discussion of the immunotoxicological effects of TCDD in a revised TA.

**Dow Comment:** Dow comments that Hong, et al., (1989) provides inconclusive results concerning immunotoxicity in rhesus monkeys. Dow indicates this study is inappropriate for development of an RfD.

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[3] WHO (World Health Organization), European Centre for Environment and Health. 1998. Executive Summary - Assessment of the health risk of dioxins: re-evaluation of the Tolerable Daily Intake (TDI). May, 1998. Geneva, Switzerland.

**Response:** Hong, et al., (1989) is discussed in the TA because this study is cited in ATSDR (1998) as the source of the lowest dose at which immunotoxic effects were noted for any test species. This reference could not be discounted without a discussion of the relevance of the findings of the study to the development of an RfD for TCDD. The ERD agrees with Dow that the findings of Hong, et al., are not sufficient to conclude that the low-dose used in this study represents the lowest dose at which immunotoxic effects have been observed in test species. Therefore, no RfD was developed from the data provided in this study.

The data used in Hong, et al., are from the same bioassay of the effects of TCDD exposure in rhesus monkeys reported in Schantz, et al., (1992) used by the ERD to support an RfD for developmental effects. While Schantz focused on neurobehavioral effects, Hong investigated immunological effects in adult female rhesus and their offspring born after TCDD exposure was discontinued. Dow provides the following quote from Hong, et al., "there appears to be no strict correlation between exposure levels and resulting body burden," and indicates that a lack of correlation would be a counter argument to the hypothesis of an immunotoxic effect. However, Dow fails to cite the sentence which follows: "Under the conditions of this study, if other immunologic effects of TCDD resulted, they occurred in animals receiving lethal doses and therefore were not detected here." Earlier in the paper the authors state, "In the 25 parts per trillion (ppt) group only 22% of offspring were alive at 1 year; there was a 50% increase in abortions, still births and infant deaths. Thus, because of fetal death, it was not possible to determine a precise immunotoxic dose separate from a lethal dose."

The findings of Hong, et al., included minimal changes in the immune system of adult females four years after termination of exposure to TCDD, however, these were not significant when compared to controls. The results of this study may have been more compelling if immunoassays had been performed while exposure was ongoing. An immunoenhancement effect was seen in two offspring of the 5 ppt group. While this effect is insufficient in itself for RfD development it is noteworthy that the same two offspring were identified by Schantz and Bowman as having behavioral deficits. To summarize, Hong, et al., suggests the possibility of immuno-logical effects at the dose levels studied, but is inconclusive due primarily to lack of viable offspring in the 25 ppt group. This information must be considered as part of the weight of evidence approach used by the ERD in identifying an appropriate RfD for noncarcinogenic effects.

RfD FOR IMMUNOTOXICITY

**Dow Comment:** Dow indicates that an RfD of 1.0E-7 mg/Kg-day for immunotoxicity is appropriate for TCDD based on data from Kociba, et al., (1978).

**Response:** The May 19, 1999 TA did not provide an RfD for immunotoxicity, primarily because other health effects for TCDD were more sensitive. The ERD will discuss the derivation of an RfD for immunotoxicity in a revised TA. However, the provision of an RfD for immunotoxicity will have no impact on the final cleanup criteria.

REPRODUCTIVE/DEVELOPMENTAL TOXICITY

**Dow Comment:** Dow asks that the TA indicate the dose levels at which effects noted in the general reproductive/developmental discussion were observed. Dow notes that many of the effects listed occur only at high doses that are inconsistent with environmental exposures.

**Response:** The database does not support Dow's position that serious effects such as offspring mortality occur only at high doses of TCDD. Female rhesus monkeys exposed to

25 ppt TCDD in-feed repeatedly failed to deliver viable offspring throughout three consecutive breedings the last of which occurred 18 months after TCDD exposure was discontinued.

Dose levels for the long list of reproductive/developmental effects of TCDD are provided in both the EPA Dioxin Reassessment and the ATSDR Toxicological Profile. The TA will refer the reader to these documents.

**Dow Comment:** Dow indicates that most reproductive/developmental studies are performed using gavage (i.e., bolus) dosing which is inconsistent with environmental exposures. In-feed or drinking water studies are the preferred dosing regime to approximate environmental exposures. Dow states that *"...more credence (should be) given to studies that would better reflect real routes of exposure (such as feeding studies)."*

**Response:** Schantz, et al. (1992) is an *in-feed* study using dose levels of *5 and 25 ppt.* Therefore, Dow's concern related to gavage dosing does not apply to the study cited in the TA as the basis for the developmental RfD. Additionally, the dose levels used in this study are not inconsistent with intake rates that could occur as a result of environmental exposures.

The ERD agrees that in-feed or drinking water studies are preferred over studies using gavage dosing to assess the effects of environmental exposure. However, data from gavage studies are not discounted and are routinely used by the ERD, the EPA, and other federal agencies for the development of toxicity endpoints for human health assessments if representative of the best available science. Gavage dosing has some advantage over in-feed or drinking water administration in that an exact quantity of compound can be reliably delivered to the test animal. Gavage dosing is also used where the compound in question renders the adulterated food or water unpalatable to the test subjects.

**Dow Comment:** Dow provides specific comments on two studies (Schantz, et al.,1989 and Bowman, et al.,1989) from "a third party outside expert."

**Response:** The ERD requests information concerning the credentials of the reviewer and the status of this individual as an outside third party. It is not clear why specific comments are provided for only these two literature articles published prior to Schantz, et al., (1992). Schantz, et al., (1992) is the study that serves as the basis for the RfD for developmental neurobehavioral effects.

**Dow Comment:** Dow states that "as indicated above" Dow "does not believe that the studies cited are appropriate for setting an RfD."

**Response:** As noted in the previous response, the literature reviews contained in Dow's comments are not for the study cited in the TA as the basis for the RfD. However, these journal articles were based on partial results from a long-term bioassay of the effects of TCDD on female rhesus monkeys and their offspring. TCDD was administered in-feed to eight female rhesus monkeys per group at doses of 5 and 25 ppt per day for four years. Initially, two other dose groups were included in the study design and received 50 and 500 ppt TCDD per day. After 2 months of dosing, 62 percent of the 500 ppt group had died. At 33 months, the 50 ppt group was discontinued because a high death rate seemed certain. The remaining two dose groups were bred with untreated males. The first offspring cohort was born after approximately 16 months of dosing. Eight of eight control females and seven of eight 5 ppt females delivered viable infants. Only one viable infant was born in the 25 ppt group. Breeding results are not reported for the second cohort. The third cohort, born 18 months after TCDD exposure

stopped, indicated improved breeding success for the 25 ppt females. Offspring were exposed to TCDD via lactation until weaning at approximately four months.

Neurobehavioral testing of rhesus offspring indicated a specific, replicable deficit in cognitive function and changes in social interactions among peer groups. Changes were also noted in the social interactions of mother-infant dyads similar to changes previously observed in lead-exposed rhesus infants. The variety and number of neurological and behavioral tests administered to the offspring in these studies is consistent with the approach recommended by several United States (U.S.) and international agencies. Because of the diverse nature of the nervous system, chemical agents can effect behavioral functions in different and specific ways. A single toxicant is not expected to produce effects and/or deficits in all areas of behavior.

Neurobehavioral deficits following prenatal exposure to TCDD have been noted in other animal species and in human offspring accidentally exposed to TCDD alone and in mixtures containing PCBs, and other dioxin-like compounds. Effects noted in exposed human offspring included persistent developmental delays, low birth-weight, persistent behavioral disorders (e.g., hyperactivity), decrease in penile length at puberty, decreased height at puberty, and hearing loss. While these data are compelling, it is not possible to determine the lowest human maternal dose of TCDD at which these effects may be present due to imprecise estimates of exposure and the confounding effects of concomitant exposure to other halogenated hydrocarbons.

The ERD uses a weight of evidence approach to identify critical effects that result from exposure to hazardous substances. Neurobehavioral effects following intrauterine and lactational exposure to TCDD have been observed in rhesus monkey offspring, the offspring of other animal species, and in human children. The U.S. Environmental Protection Agency, the U.S. Agency for Toxic Substances and Disease Registry, and the World Health Organization have recognized neurobehavioral developmental effects as one of the most sensitive endpoints of TCDD exposure. These national and international agencies have cited the Schantz and Bowman study findings in the development of a tolerable daily intake (TDI) (WHO, 1998) and a minimal risk level (MRL) (ATSDR, 1998) for TCDD exposure. The weight of evidence and the opinion of national and international experts in toxicology indicates that neurobehavioral developmental deficits are the most sensitive noncarcinogenic effect of TCDD exposure and that the findings of Schantz, et al; (1992) are appropriate for establishing an RfD for the development of Part 201 cleanup criteria.

DEVELOPMENTAL RfD

**Dow Comment:** Dow objects to the application of a 10-fold intraspecies safety factor (SF) for the protection of sensitive human individuals used in the calculation of the RfD for developmental effects. Dow states that "the application of the additional SF is a very new concept which is highly controversial," that an additional SF is not warranted because the database of pre- and post-natal toxicity is very complete, and that the data used to calculate the RfD are from a highly sensitive subpopulation (i.e., rhesus monkey infants).

**Response:** The ERD does not use the term "safety factor" in the TA. Uncertainty factors (UF) are routinely applied by both the ERD and the EPA in the development of RfDs to account for uncertainties in human health risk assessments. The application of an intraspecies UF for protection of sensitive human subjects is not a new concept: The EPA and the ERD routinely apply this UF in the calculation of all RfDs including those developed from human data. Dow appears to be confusing the routine application of the intraspecies UF with the additional 10-fold safety factor recommended in the Food Quality Protection Act (1996) when data are insufficient

to ensure protection for children. The ERD is not proposing the application of this additional safety factor for the protection of children. An additional factor, beyond the traditional intraspecies UF, is not deemed necessary because the study which serves as the basis for the RfD considered effects in offspring of exposed rhesus mothers.

BACKGROUND EXPOSURES

**Dow Comment:** Dow objects to the use of the relative source contribution (RSC) factor for the development of the soil direct contact criteria as an attempt at a multi-pathway risk assessment. Dow also objects to the use of the RSC for noncarcinogenic endpoints only.

**Response:** As stated in the cover letter, Part 201 provides for the application of a factor to account for "source contributions" other than the pathway under consideration in the development of soil cleanup criteria and specifies a default value of one (100 percent) unless data are available to justify a chemical-specific value. Consideration of source contribution for carcinogenic effects is not provided for under Part 201.

The available data indicate that TCDD and related compounds are ubiquitous in the diet of U.S. residents: some studies indicate that average dietary exposures likely exceed the ERD RfD and the ATSDR MRL. Taken at face value, these data indicate that no additional exposure to TCDD beyond dietary sources is prudent for the protection of public health. However, uncertainties in dietary data prompted the ERD to choose a less conservative RSC of 80 percent for dietary exposure, leaving 20 percent of the acceptable dose for development of the soil direct contact criteria.

Data quantifying exposure to hazardous substances other than TCDD are generally unavailable. The ERD applies exposure data where available and of sufficient quality to choose an appropriate RSC. Data are available for TCDD primarily due to the toxic nature of this compound and public concerns related to its health effects.

EXPOSURE VALUES FOR DEVELOPMENTAL EFFECTS

**Dow Comment:** Dow makes reference to the EPA's *Guidelines for Reproductive Toxicity Risk Assessment* (September 1996) and the 1992 Habicht memo.

**Response:** The reference to the 1996 EPA document should actually be for the EPA's Guidelines for Developmental Toxicity Risk Assessment (EPA, 1991). The issue of the overly conservative generic exposure assumption is addressed in the cover letter and in the attached tables. Tables 1 through 4 present all of the generic exposure assumptions used to develop residential soil direct contact criteria for carcinogenic hazardous substances. The table presents Dow's characterization of the parameters and the ERD's response.

PART 201 CLEANUP DIRECT CONTACT CRITERIA FOR SOILS

**Dow Comment:** Dow indicates there may be mathematical errors in the calculation of soil direct contact criteria and questions the accuracy of the soil adherence factors used in these calculations.

**Response:** There are no mathematical errors in the calculation of soil direct contact criteria presented on page 7 of the TA. There is, however, a typographical error on page 9 of the TA: the RfD listed in the table directly below the criterion algorithm is incorrectly given as 1E-9 mg/Kg-day. This value should be 1.3E-9 mg/Kg-day as indicated in the text on page 5. Presumably, this error led to Dow's confusion.

Default soil adherence factors used in the calculation of soil direct contact criteria are correct as listed on page 8 of the TA. The document referenced for these values (ERD, 1999 as shown in the reference section of the TA) has been distributed to the Part 201 Program Advisory Group (including Dow). Dow's July 9, 1999 "Comments on the Proposed Modifications of Part 201 Direct Contact Criteria" indicate support for these values. Adherence factor values were inadvertently left out of the tables on page 9 and will be added to the final TA.

**Dow Comment:** Dow comments in a table format on the ERD generic assumptions for calculation of Part 201 soil direct contact criteria.

**Response:** Dow's specific comments and the ERD associated responses are provided in Tables 1 through 4.

PART 201 DRINKING WATER CRITERIA FOR GROUNDWATER

**Dow Comment:** Dow suggests deleting the section describing the basis for the Part 201 Drinking Water Criteria for Groundwater.

**Response:** The ERD Toxicological Assessments serve the primary function of documenting criteria development for both staff and the interested public. When a criterion deviates from the value that would be calculated using the generic approach described in the applicable Part 201 Technical Support Document (TSD), the reason for the deviation must be documented. Part 201 requires that a State Drinking Water Standard, if available, be adopted as the Part 201 drinking water criterion. The State standard may differ from the value which could be calculated using the Part 201 generic approach and the oral slope factor and/or reference dose given in the TA. This section is included, therefore, to reduce any potential confusion as to the source of the Part 201 drinking water criterion for TCDD.

UNCERTAINTY

**Dow Comment:** Dow asks for clarification on the uncertainty associated with the effect of body burden on calculation of soil DCC.

**Response:** The ERD will expand on the discussion of uncertainty in a revised TA and include additional language clarifying the role of TCDD body burden in the derivation of Part 201 cleanup criteria.

**Dow Comment:** Dow requests that a discussion of the uncertainty associated with the generic DCC calculation be included in the TA. Dow repeats their previously expressed opinion that the generic DCC are overly conservative.

**Response:** This comment is directed to the generic process for DCC calculation rather than to the chemical-specific issues related to the development of toxicity values for TCDD. The ERD Toxicological Assessments are not the appropriate forum to address these generic issues. The uncertainty related to generic criteria calculation is best addressed in the Part 201 technical support documents (TSDs) published by the ERD. To repeat this generic discussion of uncertainty in every chemical-specific TA would be redundant and inefficient. This issue is also addressed in previous responses related to the generic exposure assumptions.

TOXIC EQUIVALENCY FACTORS

**Dow Comment:** Dow comments on the Toxic Equivalency Factor (TEF) approach for TCDD and other dioxin-like compounds and suggests that the approach overestimates the actual

toxicity of combined congener exposure. Dow indicates that abandonment of the TEF approach is not necessary to address these concerns.

**Response:** The ERD agrees that the TEF approach should not be abandoned. While, this approach is considered interim by the EPA, it has been approved by the WHO and the North Atlantic Treaty Organization's Committee on Challenges of Modern Society.

The ERD disagrees with Dow's suggestion that the TEF approach overestimates the actual toxicity of combined congener exposure. In June of 1997 the WHO organized a meeting of international experts in the field of toxicology to review and update the TEF approach. While recognizing the associated uncertainties, the WHO review concluded "that the TEF concept is still the most plausible and feasible approach for risk assessment of halogenated aromatic hydrocarbons with dioxin-like properties." Further, the review concluded "it is unlikely for the use of this additive model to result in a great deal of error in predicting the concentrations of TCDD TEQs [toxic equivalents] or responses at environmentally relevant levels due to nonadditive interactions." The later conclusion is based on the results of studies comparing the toxicity of mixtures of dioxin-like compounds to that of individual congeners. The WHO review concluded that additivity is the most likely type of interaction between dioxin-like compounds.[4]

[4] Van den Berg, et al. 1998. Toxic Equivalency Factors (TEFs) for PCBs, PCDDs, PCDFs for Humans and Wildlife. Environmental Health Perspectives, Vol. 106, No. 12.

**R 299.5750 Footnotes for generic cleanup criteria tables.**

**Rule 750.** (1) The footnotes that apply to the generic criteria tables in R 299.5744, R 299.5746, and R 299.5748 are as follows:

(A) Criterion is the state of Michigan drinking water standard established pursuant to section 5 of 1976 PA 399, MCL 325.1005.

(B) Background, as defined in R 299.5701(b), may be substituted if higher than the calculated cleanup criterion. Background levels may be less than criteria for some inorganic compounds.

(C) Value presented is a screening level based on the chemical-specific generic soil saturation concentration (Csat) since the calculated risk-based criterion is greater than Csat. Concentrations greater than Csat are acceptable cleanup criteria for this pathway where a site-specific demonstration indicates that free-phase material containing a hazardous substance is not present.

(D) Calculated criterion exceeds 100%, hence it is reduced to 100% or 1.0E+9 ppb.

(E) Criterion is the aesthetic drinking water value, as required by section 20120a(5) of the act. A notice of aesthetic impact may be employed as an institutional control mechanism if groundwater concentrations exceed the aesthetic drinking water criterion, but do not exceed the applicable health-based drinking water value provided in the following table:

| Hazardous Substance | Chemical Abstract Service Number | Residential Health-Based Drinking Water Value | Industrial-Commercial Health-Based Drinking Water Value |
|---|---|---|---|
| Aluminum | 7429905 | 300 | 4,100 |
| tertiary Amyl methyl ether | 994058 | 910 | 2,600 |
| Copper | 7440508 | 1,400 | 4,000 |
| Diethyl ether | 60297 | 3,700 | 10,000 |
| Ethylbenzene | 100414 | 700 | 700 |
| Iron | 7439896 | 2,000 | 5,600 |
| Manganese | 7439965 | 860 | 2,500 |
| Methyl-tert-butyl ether (MTBE) | 1634044 | 240 | 690 |
| Toluene | 108883 | 1,000 | 1,000 |
| 1,2,4-Trimethylbenzene | 95636 | 1,000 | 2,900 |
| 1,3,5-Trimethylbenzene | 108678 | 1,000 | 2,900 |
| Xylenes | 1330207 | 10,000 | 10,000 |

(F) Criterion is based on adverse impacts to plant life and phytotoxicity.

(G) Groundwater surface water interface (GSI) criterion depends on the pH or water hardness, or both, of the receiving surface water. The final chronic value (FCV) for the protection of aquatic life shall be calculated based on the pH or hardness of the receiving surface water. Where water hardness exceeds 400 mg $CaCO_3$/L, use 400 mg $CaCO_3$/L for the FCV calculation. The FCV formula provides values in units of ug/l or ppb. The generic GSI criterion is the lesser of the calculated FCV, the wildlife value (WV), and the surface water human non-drinking water value (HNDV). The soil GSI protection criteria for these hazardous substances are the greater of the

(L) Criteria for lead are derived using a biologically based model, as allowed for under section 20120a(10) of the act, and are not calculated using the algorithms and assumptions specified in pathway-specific rules. The generic residential drinking water criterion of 4 ug/l is linked to the generic residential soil direct contact criterion of 400 mg/kg. A higher concentration in the drinking water, up to the state action level of 15 ug/l, may be allowed as a site-specific remedy, and still allow for drinking water use, under section 20120a(2) of the act if soil concentrations are appropriately lower than 400 mg/kg. If a site-specific criterion is approved based on this subdivision, a notice shall be filed on the deed for all property where the groundwater concentrations will exceed 4 ug/l to provide notice of the potential for unacceptable risk if soil or groundwater concentrations increase. Acceptable combinations of site-specific soil and drinking water concentrations are presented in the following table:

**Acceptable Combinations of Lead in Drinking Water and Soil**

| Drinking Water Concentration (ug/L) | Soil Concentration (mg/kg) |
|---|---|
| 5 | 386-395 |
| 6 | 376-385 |
| 7 | 376-385 |
| 8 | 366-375 |
| 9 | 356-365 |
| 10 | 346-355 |
| 11 | 336-345 |
| 12 | 336-345 |
| 13 | 326-335 |
| 14 | 316-325 |
| 15 | 306-315 |

(M) Calculated criterion is below the analytical target detection limit, therefore, the criterion defaults to the target detection limit.

(N) The concentrations of all potential sources of nitrate-nitrogen (e.g., ammonia-N, nitrite-N, nitrate-N) in groundwater that is used as a source of drinking water shall not, when added together, exceed the nitrate drinking water criterion of 10,000 ug/l. Where leaching to groundwater is a relevant pathway, soil concentrations of all potential sources of nitrate-nitrogen shall not, when added together, exceed the nitrate drinking water protection criterion of 2.0E+5 ug/kg.

(O) The concentration of all polychlorinated and polybrominated dibenzodioxin and dibenzofuran isomers present at a facility, expressed as an equivalent concentration of 2,3,7,8-tetrachlorodibenzo-p-dioxin based upon their relative potency, shall be added together and compared to the criteria for 2,3,7,8-tetrachlorodibenzo-p-dioxin. The generic cleanup criteria for 2,3,7,8-tetrachlorodibenzo-p-dioxin are not calculated according to the algorithms presented in R 299.5714 to R 299.5726. The generic cleanup criteria are being held at the values that the department has used since August 1998, in recognition of the fact that national efforts to reassess risks posed by dioxin are not yet complete. Until these studies are

complete, it is premature to select a revised slope factor and/or reference dose for calculation of generic cleanup criteria.

(P) Amenable cyanide methods or method OIA-1677 shall be used to quantify cyanide concentrations for compliance with all groundwater criteria. Total cyanide methods or method OIA-1677 shall be used to quantify cyanide concentrations for compliance with soil criteria. Industrial/commercial direct contact criteria may not be protective of the potential for release of hydrogen cyanide gas. Additional land or resource use restrictions may be necessary to protect for the acute inhalation concerns associated with hydrogen cyanide gas.

(Q) Criteria for carcinogenic polycyclic aromatic hydrocarbons were developed using relative potential potencies to benzo(a)pyrene.

(R) Hazardous substance may exhibit the characteristic of reactivity as defined in 40 C.F.R. §261.23 (revised as of July 1, 2001), which is adopted by reference in these rules and which is available for inspection a the Lansing office of the Department, 525 West Allegan Street, Lansing, Michigan. Copies of the regulation may be purchased, at a cost as of the time of adoption of these rules of $45.00, from the Superintendent of Documents, Government Printing Office, Washington, DC 20401 (stock number 869-044-00155-1), or from the Department of Environmental Quality, Remediation and Redevelopment Division, 525 West Allegan Street, Lansing, MI 48933, at cost.

(S) Criterion defaults to the hazardous substance-specific water solubility limit.

(T) Refer to the federal toxic substances control act (TSCA), 40 C.F.R. §761, Subpart D and 40 C.F.R. §761, Subpart G, to determine the applicability of TSCA cleanup standards. Subpart D and Subpart G of 40 C.F.R. §761 (July 1, 2001), are adopted by reference in these rules and are available for inspection a the Lansing office of the department, 525 West Allegan Street, Lansing, Michigan. Copies of the regulations may be purchased, at a cost as of the time of adoption of these rules of $55.00, from the Superintendent of Documents, Government Printing Office, Washington, DC 20401, or from the Department of Environmental Quality, Remediation and Redevelopment Division, 525 West Allegan Street, Lansing, MI 48933, at cost. Alternatives to compliance with the TSCA standards listed below are possible under 40 C.F.R. §761 Subpart D. New releases may be subject to the standards identified in 40 C.F.R. §761, Subpart G. Use part 201 soil direct contact cleanup criteria in the following table if TSCA standards are not applicable:

**Summary of Public Comments and Department of Environmental Quality (DEQ) Responses Regarding Proposed Rules for Part 201, Environmental Remediation, of the Natural Resources and Environmental Protection Act, 1994 PA 451, as amended (the Act) for the Public Comment Period Ending March 25, 2002**

Key to Commentors:

ADS = Adrian Dominican Sisters
Bardenstein = Renah Bardenstein
BBL =Blasland, Bouck & Lee, Inc.
Buckner = Kathryn A. Buckner
Bursian = Steve Bursian
DAG = Department of Attorney General
Dempsey = Dave Dempsey
Detroit = City of Detroit
Dow = Dow Chemical Company
EC = Ecology Center
EMEAC = East Michigan Environmental Action Council
Holmes = Peter D. Holmes
GM = General Motors
Gonzales = Roy Gonzales
GR = City of Grand Rapids
GRCC = Grand Rapids Chamber of Commerce
Henke = Dellas Henke
ICHD = Ingham County Health Department
JCHD = Jackson County Health Department
KPC = Kingsford Products Company
LMF = Lake Michigan Federation
LTC = Lone Tree Council
Mallonee = Donna Mallonee
McGowan = Blair J. McGowan
MEC = Michigan Environmental Council
MCC = Michigan Chemistry Council
MHC = Michigan Housing Council (by Richard Barr)
MMA = Michigan Manufacturers Association
MMEAC = Mid-Michigan Environmental Action Council
MOGA = Michigan Oil and Gas Association
MPPEC = Michigan Pulp and Paper Environmental Council
O'Connell = Thomas O'Connell
O'Reilly = Daniel O'Reilly
Patterson = Jarrold Patterson
Pillepich = Larry Pillepich
Roth = Peggy Roth
SEMCOG = Southeast Michigan Council of Governments
SCC = Stone Container Corporation
SMD = Sisters of Mercy Regional Community of Detroit
Stamiris = Barbara Stamiris
Stone = Evan L. Stone
Sunderman = Travis Sunderman
Taylor = John Taylor
Tripp = David L. Tripp
USEPA = U.S. Environmental Protection Agency Region 5

| RULE | SUBRULE | COMMENT | RESPONSE | COMMENTOR |
|---|---|---|---|---|
| Overall | | Commentor objects to length of public comment period. | Public comment period exceeded the minimum requirements of the Administrative Procedures Act, 1969 PA 306, as amended (APA). | GRCC |

| RULE | SUBRULE | COMMENT | RESPONSE | COMMENTOR |
|---|---|---|---|---|
| 744,<br>746,<br>748,<br>750,<br>752 | | Commentors object to cleanup criteria for dioxin compounds. | The cleanup criteria for 2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,3,7,8-tetrabromodibenzo-p-dioxin ("dioxin") have been changed. The department recognizes that a national reassessment of the risks posed by dioxin is underway and that the results of that reassessment will likely result in changes in cleanup criteria for dioxin. However, the department does not believe it is appropriate at this time to base cleanup criteria on the pending reassessment. As a result, the cleanup criteria presented in the rules are the cleanup criteria that have been used by the department since August 1998. These criteria are not based on the same exposure assumptions that are used for calculation of other cleanup criteria. To account for this, the footnote for dioxin (footnote (O)) has been modified to note that dioxin criteria do not conform to the relevant rules for calculation of other cleanup criteria. It is the department's judgment that maintaining the current level of protection for dioxin is the most prudent course until the reassessment is complete. Using the up-to-date exposure factors in the rules in combination with the current toxicological inputs would result in higher criteria (i.e., the criteria that were presented in the February 11, 2002, proposed rules). The department will continue to monitor the dioxin reassessment and the available information about dioxin and will propose modification to the dioxin cleanup criteria, if appropriate, in a future revision of the cleanup criteria. | ADS, Bardenstein, Bursian, DAG, Dempsey, EC, EMEAC, Gonzales, Henke, LMF, LTC, Mallonee, McGowan, MEC, MMEAC, O'Connell, O'Reilly, Pillepich, Roth, SMD, Stamiris, Stone, Sunderman, Taylor, USEPA |

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY (MDEQ)
ENVIRONMENTAL RESPONSE DIVISION (ERD)

Part 201

# TOXICOLOGICAL ASSESSMENT AND PART 201 CLEANUP CRITERIA FOR 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN AND RELATED COMPOUNDS

May 19, 1999

Linda D. Larsen, Ph.D.

## EXECUTIVE SUMMARY

TCDD and related compounds have been shown to cause a wide variety of adverse effects in experimental animals and in exposed human populations. Observed effects in experimental animals are diverse and include lethality, cancer, immunotoxicity, hepatotoxicity, dermal toxicity, endocrine disruption, reproductive and developmental effects, and enzyme induction. Many of these effects have been observed in human populations exposed to TCDD and related compounds in occupational settings or through accidental release to the environment. Part 201 of Act 451 requires that cleanup criteria be developed to be protective of the most sensitive effect considering cancer and any other noncarcinogenic effects. The current MDEQ review focuses on potential carcinogenicity and the three noncarcinogenic endpoints identified as the most sensitive for TCDD and related compounds: hepatotoxicity (liver toxicity), immunotoxicity (adverse effects in the immune system), and reproductive/developmental toxicity. Developmental neurobehavioral alterations in rhesus monkeys occurs at lower daily doses than either hepatotoxicity or immunotoxicity and is, therefore, the most sensitive noncarcinogenic effect.

A comparison of the Part 201 soil direct contact criteria (DCC) protective of cancer to the DCC protective of developmental neurobehavioral effects indicates that the most sensitive effect differs for residential and non-residential land uses. For residential land use, the DCC will be based on protection for carcinogenic effects: the Part 201 generic residential DCC is 0.23 ug/Kg. For non-residential land use, the DCC will be based on protection for noncarcinogenic developmental neurobehavioral effects: the Part 201 generic industrial DCC is 0.36 ug/Kg. Part 201 generic commercial DCC will be developed at a later date. The most sensitive effect differs between land uses because the generic exposure assumptions used to calculate DCC differ between residential and non-residential land uses. The Part 201 drinking water criteria for all land uses is the state drinking water standard of 3.0E-5 ug/L per section 324.20120a(5) of Part 201 of Act 451.

## INTRODUCTION

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is the representative prototype of a class of structurally related compounds that are ubiquitous and persistent in the environment. The basic structure of these compounds is a double benzene ring joined at the *para* carbon positions with 2 oxygen atoms. Halogens, generally either chlorine or bromine, may be substituted at the four remaining carbon positions on each benzene ring. Monohalogenated through octahalogenated congeners of the dibenzo-p-dioxins are therefore possible. Research into the toxic effects of these compounds has focused primarily on congeners with halogens at the four lateral carbon positions. 2,3,7,8-tetrachlorodibenzo-p-dioxin or TCDD, with all four lateral positions occupied by chlorine, is considered the most toxic of the dibenzo-p-dioxins and related compounds. The toxicity of other dibenzo-p-dioxins, related compounds such as dibenzo-p-furans, and coplanar polychlorinated biphenyls are assessed relative to the potency of TCDD (ATSDR, 1998).

The toxicity of TCDD and related compounds has been extensively reviewed by the Environmental Protection Agency (EPA), Office of Research and Development and the U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry

(ATSDR). EPA has released its preliminary findings in two "external review draft" multi-volume documents entitled "Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds" (June 1994) (EPA,1994b) and "Estimating Exposure to Dioxin-Like Compounds" (June 1994) (EPA,1994a). These documents are commonly referred to as EPA's "Dioxin Reassessment." Chapter 8 of the draft Health Assessment Document was revised in January of 1997 (EPA, 1997b). However, a final version of the Dioxin Reassessment has not yet been released. ATSDR's review is contained in the updated "Toxicological Profile for Chlorinated Dibenzo-p-Dioxins" (December 1998) (ATSDR, 1998). The ATSDR profile is considered final. The following MDEQ review relies primarily on these documents, supplemented by original key studies from the scientific literature as necessary.

NOTE: This review does not address inhalation exposures to TCDD or TCDD-related compounds.

TCDD and related compounds have been shown to cause a wide variety of effects in experimental animals and in exposed human populations. Observed effects in experimental animals are diverse and include lethality, cancer, immunotoxicity, hepatotoxicity, dermal toxicity, endocrine disruption, reproductive and developmental effects, and enzyme induction. Information on human health effects comes from occupational exposures or from populations exposed due to accidental releases or contamination of the food supply. Human studies are difficult to interpret due to incomplete information regarding dose, concomitant exposure to other compounds, and the limited number of people exposed (ATSDR, 1998). Therefore, the remainder of this review will focus on effects observed in experimental animals. However, preliminary data obtained from the study of exposed human populations indicates that many of the effects noted in experimental animals also occur in humans (Birnbaum, 1995; DeVito et al, 1995; Grassman et al, 1998).

## TOXICOLOGICAL REVIEW

The EPA Dioxin Reassessment and the ATSDR Toxicological Profile provide exhaustive reviews of the available scientific literature reporting on the toxic effects of TCDD. These documents are recommended for additional reading. The current MDEQ review will focus on potential carcinogenicity and the three noncarcinogenic endpoints that have been identified as the most sensitive for TCDD and related compounds: hepatotoxicity (liver toxicity), immunotoxicity (adverse effects in the immune system), and reproductive/developmental toxicity.

### Mechanism of Action

Early investigation into the toxic effects of TCDD yielded seemingly paradoxical results. Effects varied widely between species, between strains of the same test species, and between tissues in the same test animal. Recent research has indicated that the effects of TCDD are mediated through binding to the intracellular protein known as the aryl hydrocarbon (Ah) receptor. Binding of TCDD with the Ah receptor is stereospecific, meaning that only compounds of similar chemical structure and three dimensional configuration will bind to the receptor and produce activation of the responses it mediates (EPA, 1994b). The Ah receptor is believed to be the first step in activation of a group of proteins that regulate mRNA mediated enzyme and protein production in the cell nucleus. The Ah receptor is also believed to function in the cytoplasm as a regulator of second messenger proteins (Birnbaum, 1995). These proteins act as chemical messengers, conveying information from receptor sites near the cell membrane to the nucleus where various cellular support mechanisms are regulated. These cellular functions are intrinsically involved in cell growth, viability, proliferation, differentiation, and cell death. The variation in effects of dioxins across strain and species and even between tissues of the same

organism may, therefore, be attributed to genetic and functional variation in the role of the Ah receptor and the diversity of the responses it mediates.

## Carcinogenicity

TCDD has been shown to be multisite carcinogenic in mice and rats in several chronic bioassays for carcinogenicity, the most important of which are the Kociba et al. (1978) and National Toxicology Program (1982) studies. Carcinogenicity has also recently been demonstrated in the hamster, considered to be the most resistant species to the acute toxic effects of TCDD (EPA, 1994b). The Kociba 1978 assay in Sprague-Dawley rats is the basis for the oral carcinogenic slope factor calculated by EPA and MDEQ and is summarized below.

Kociba et al. (1978) administered TCDD to 50 rats per sex per group in-feed at doses of 0.001, 0.01, and 0.1 ug TCDD/Kg of body weight per day for 2 years. The control group of 86 male and 86 female rats were administered the vehicle alone. The findings of this study relative to carcinogenesis include increases in hepatocellular hyperplastic nodules and hepatocellular carcinomas in female rats, squamous cell carcinomas of the nasal turbinates, hard palate and tongue in male rats, and lung tumors in high-dose female rats. The liver tumor incidence in female rats was significantly elevated above control animals at the 0.01 ug TCDD/Kg dose level and showed clear evidence of a dose-response relationship. Lung tumors in female rats were significantly elevated in the high-dose group. The increased incidence of squamous cell carcinomas of the nasal turbinates, hard palate and tongue in male rats was significant in the low-dose group, but no evidence of a dose-response relationship was apparent. Liver and lung tumors were not observed in male rats.

In 1990 an independent panel of seven pathologists under the direction of the U.S. Food and Drug Administration and the EPA, reevaluated the female liver slides according to the National Toxicology Program's 1986 liver tumor classification scheme. These results, combined with the previously noted incidences of lung tumors in female rats and tumors of the nasal turbinates, hard palate and tongue in male rats, formed the basis for the oral slope factor of 7.5E+4 $(mg/Kg\text{-}day)^{-1}$ previously developed by MDEQ (MDEQ, 1990). This value is derived from the calculated animal cancer potency value from the Kociba study (1978) multiplied by a species scaling factor of the human body weight to the test species weight raised to the 2/3 power to account for the differences between humans and test species. Consistent with the EPA's proposed 1996 Cancer Risk Assessment Guidelines and the Administrative Rules promulgated pursuant to Part 31of Act 451, ERD is implementing a revised species scaling factor of the human body weight to the test species weight raised to the 3/4 power for the calculation of Part 201 cleanup criteria for carcinogenic compounds. The oral slope factor based on the combined tumor incidence rate observed from Kociba (1978) and using the revised species scaling factor is 4.9E+4 $(mg/Kg\text{-}day)^{-1}$.

## Noncarcinogenic Effects of TCDD

Three noncarcinogenic endpoints have been identified as the most sensitive for TCDD and related compounds: hepatotoxicity (liver toxicity), immunotoxicity (adverse effects in the immune system), and reproductive/developmental toxicity. Observed adverse effects and the key study chosen for the development of an oral references dose (RfD) for each endpoint are discussed below.

## Hepatotoxicity

Numerous systemic effects have been noted following oral administration of TCDD to experimental animals. Effects observed include increased mortality, focal alveolar hyperplasia in the respiratory system, myocardial degeneration, hematological changes, renal effects, toxic

hepatitis, hepatocellular alterations and hepatic necrosis, dermatitis, and decreased body weight gain. Of these, hepatotoxicity appears to be the most sensitive effect.

The Kociba (1978) study discussed above is the basis for the oral reference dose for hepatotoxic effects. Increased mortality was seen in high dose females, but not in high dose males or in either males or females at lower dose levels. Mean body weights decreased for all high-dose animals from month 6 to the end of the study. Decreased body weight was also observed in mid-dose females, but to a lesser extent. Histological examination of rats surviving to the end of the study indicated multiple degenerative, inflammatory and necrotic changes in the liver. These effects were more extensive in females. Liver damage was dose-related in mid-and high-dose groups, no effects were observable in low-dose groups.

**RfD for Hepatotoxicity** - The no observed adverse effect level (NOAEL) for this study is 0.001 ug/Kg-day or 1.0E-6 mg/Kg-day. Application of an uncertainty factor of 100 (10 for interspecies extrapolation, 10 to account for sensitive human individuals) yields an oral RfD for hepatotoxicity of 1.0E-8 mg/Kg-day.

**Immunotoxicity**

The database describing the immunotoxic effects of TCDD and related compounds is extensive. High doses of TCDD have been shown to produce atrophy of the thymus. Effects at lower doses include: suppression of T-cell immunity, delayed hypersensitivity responses, increased susceptibility to infectious disease, and alterations in immune effector functions. The available database, however, is not adequate to provide the basis for cross species comparability of effects and dose. Recent advances suggest this is due to variability in the binding affinity of TCDD to the Ah receptor believed to mediate the immunotoxic effects of TCDD. Strains of mice that exhibit genetic differences in Ah receptor function show significant differences in immunosuppresion following administration of TCDD and/or related compounds. In addition, TCDD congeners that show greater binding affinity for the Ah receptor have been shown to be more potent in eliciting immunosuppressive responses than congeners with relatively less affinity for the Ah receptor.

**RfD for Immunotoxicity** – Thymic atrophy was observed in high-dose rats in Kociba et al. (1978). The NOAEL for this effect is 0.01 ug/Kg/day. Hong et al. (1989) reported immune abnormalities in offspring of rhesus monkeys exposed prenatally and lactationally to TCDD. The test subjects were the same individuals used in the Schantz et al. 1992 study described below. However, the NOAEL identified by ATSDR (1998) for immunotoxicity from this study is inconsistent with the dose levels reported in Schantz et al. (1992). Since, however, Hong reported no adverse immunotoxic effects in low-dose offspring, it may be concluded that the RfD for developmental effects described below based on the lowest dose administered in the Schantz study is protective of potential immunotoxic effects.

**Reproductive /Developmental Toxicity**

TCDD administered to experimental animals has been shown to cause adverse effects in both male and female reproductive symptoms. Effects observed in females include: decreases in ovarian weight, altered estrus cycle and ovulation, pre- and post-implantation fetal loss, reduced fertility, and alterations in levels of circulating hormones. Effects observed in males include: decreased testis and accessory organ weights, abnormal testicular morphology, decreased spermatogenesis, reduced fertility, and reduced levels of androgenic hormones. Developmental effects in offspring of TCDD exposed female animals include: mortality; structural malformations such as cleft palate and hydronephrosis; thymic atrophy; immunosuppression; structural and function impairment of the reproductive system; intestinal, subcutaneous and brain hemorrhages; decreased growth; and neurobehavioral alterations. Effects in offspring occurred

following TCDD administration to dams prior to mating, during gestation, and during lactation. Fetal death has occurred in several experimental animals, including monkeys, at doses that caused no apparent maternal toxicity. Structural defects in mice have been observed at doses that caused no apparent maternal or fetal toxicity. Of these observed effects, neurobehavioral alterations in rhesus monkeys (Schantz et al., 1992) is the most sensitive and was used by ATSDR to develop a chronic minimal risk level (MRL) of 1.0E-9 mg/Kg-day for daily human exposure.

Schantz et al. (1992) administered TCDD to groups of eight rhesus monkeys at doses of 0, 5, and 25 part per trillion (ppt) in-feed for a total of 16.2±0.4 months. Monkeys were mated after 7 months of exposure to an unexposed male. Seven of eight high-dose monkeys failed to deliver viable offspring, therefore, only offspring on the 5 ppt group were available for behavioral studies. TCDD administration continued throughout gestation and lactation. Offspring were weaned at age 4 months. At 8.6 months of age, offspring were placed in peer groups of two dosed and two control monkeys. Behavioral patterns in a play room were observed for 1.5 hours per day, 4 days per week for 9 weeks. Significant alterations were observed in play behavior, displacement behavior, and self-directed behavior in the dosed offspring as compared to controls. Dosed offspring tended to initiate rough play more often, to retreat from rough play less often, and were less often displaced from preferred positions in the play area. Dosed offspring also tended to engage in self-directed behavior more often than controls. This behavior is defined as oral, manual or pedal self-manipulation and is considered to be a maladaptive behavioral pattern. This pattern of behavior is characteristic of monkeys reared in conditions of social deprivation and is consistent with a similar pattern of behavior in emotionally disturbed human children. The authors postulated that the observed increase in both adaptive and maladaptive social behaviors may be indicative of an increase in the overall level of behavioral arousal.

**Developmental RfD** - A NOAEL could not be identified for this study. The lowest observed adverse effect level (LOAEL) of 5 ppt is converted to 1.3E-4 ug/Kg-day (1.3E-7 mg/Kg-day) using the food consumption rate of 0.19 Kg/day (Schantz et al. 1992) and a maternal body weight of 7.5 Kg (Bowman et al. 1989). A $10^{0.5}$ UF is applied to account for the use of a minimal LOAEL since the observed neurobehavioral effects are not of marked severity. A $10^{0.5}$ UF is applied for extrapolation from monkeys to humans. A full10-fold factor for interspecies extrapolation is not considered necessary because of similarities in toxic responses and general physiology between monkeys and humans. An additional UF of 10 is applied to account for sensitive human individuals. Application of the total UF of 100 ($10^{0.5}$ x $10^{0.5}$ x 10) yields an oral RfD of 1.3E-9 mg/Kg-day.

The total UF of 100 used to develop the RfD for Part 201 criteria calculations differs from the UF of 90 presented in the ATSDR Toxicological Profile. ATSDR used UFs of 3 for use of a minimal LOAEL, 3 for interspecies extrapolation, and 10 to account for sensitive human individuals. The use of a 3-fold UF is not consistent with the logarithmic basis of uncertainty factor development. Therefore, the more appropriate value of $10^{0.5}$, rather than 3, has been used here to represent the mid-point between 1 and 10 on a logarithmic scale (Dourson, 1994; Swartout, 1999).

## BACKGROUND EXPOSURES

Chapter 5 of Estimating Exposure to Dioxin-Like Compounds (EPA, 1994a) provides an assessment of background exposures to TCDD and related compounds. This assessment uses national average concentrations of TCDD and related compounds in air, drinking water, soil, and in the food supply to estimate the background levels to which U.S. citizens may be exposed. Intake rates for food products were estimated using data from the U.S. Department of Agriculture's (USDA) report on "Food Consumption, Prices, and Expenditures between 1970

and 1992" and the USDA's "National Food Consumption Survey" (1992). Food products considered include milk, dairy, eggs, beef, pork and poultry. This study indicates that the average U.S. citizen is exposed via these food products to approximately 110 picograms of TCDD and related compounds per day (1.6 pg/Kg of body weight/day assuming a 70 Kg adult).

The estimated background value of 1.6 pg/Kg/day given above falls roughly at the mid-point of the range of 0.3 pg/Kg/day to 3.0 pg/Kg/day (18-192 pg/day) for daily intake rates reported by Schecter et al. (1994). Schecter used a concentration range of TCDD and related compounds in foods purchased in New York state rather than an average concentration to calculate the levels to which a 65 Kg adult may be exposed. While only foods purchased in New York were used in this study, the results may be generally applicable since food supplies in the U.S. may be shipped long distances and most major brands are marketed nationally. The concentration range used in this study may be preferable to the averaging technique used by EPA (1994a). In the EPA study, samples with no detectable TCDD or related compounds were reported for the purposes of averaging to have concentrations at the detection limit of the analysis. This approach may be faulty since the data are insufficient to conclude that all food products of the type sampled will contain some, albeit undetected, level of TCDD or related compounds.

Section 20120a(4) of Part 201 of Act 451 states, "For the noncarcinogenic effects of a hazardous substance present in soils, the intake shall be assumed to be 100% of the protective level, unless compound and site-specific data are available to demonstrate that a different source contribution is appropriate." The above discussion indicates that TCDD and related compounds are present in nationally available food products that are commonly consumed on a daily basis by the average U.S. citizen. However, the data are insufficient at this time to more precisely predict the levels at which these or other non-soil exposures may occur. It is therefore assumed that 80% of the average exposure to TCDD and related compounds occurs from a source other than exposure to contaminated soils. Therefore, Part 201 soil direct contact criteria for TCDD and related compounds protective of noncarcinogenic effects are calculated employing a 20% relative source contribution factor (RSC).

## EXPOSURE ASSUMPTIONS AND CRITERIA CALCULATION

### Exposure Values for Carcinogenic Effects

For carcinogenic compounds, exposures are calculated by prorating the total cumulative dose over a lifetime of 70 years (also called lifetime average daily dose). The approach for carcinogens is based on the assumption that a high dose of a carcinogen received over a short period of time is equivalent to a corresponding low dose spread over a lifetime. Part 201 residential DCC assume that exposure occurs over a 30 year exposure duration at an exposure frequency of 350 days/year. Intake of soil via the soil incidental ingestion and dermal direct contact pathways is age-adjusted to account for behaviors in children that result in higher exposure. Part 201 industrial DCC assume that exposure occurs over a 21 year exposure duration at an exposure frequency of 245 days/year for ingestion and 112 days/year for dermal contact. Children are not assumed to be present on industrial property.

### Exposure Values for Developmental Effects

The noncarcinogenic Part 201 DCC protective of developmental effects for all land uses are intended to be protective of a pregnant female adult and her developing fetus. The timing of exposure to developmental toxicants may affect both the type and severity of effect on the developing organism. Some compounds may exert these effects after only a single exposure, while others may require a longer period of exposure before effects are manifested. For example, blastocyst formation and implantation occur in 1 to 2 days (day 3-5 post fertilization) in most mammalian species including humans. A single dose of a compound that interferes with

these processes may result in arrested development of the embryo and probable lethality. The period of organogenesis during which primitive cells divide and association into organ rudiments typically lasts for several days, ranging from 6-15 days post fertilization in rodents to days 21-56 in humans. During this 35 day period in humans, individual organ systems may be more or less susceptible on any given day and critical periods for each system may show considerable overlap. Structural defects are often the result of exposure during this time, but functional effects may also be noted. Growth retardation and functional impairment may also result from exposure during the fetal and neonatal period following organogenesis. Unfortunately, little is known about the critical period during which most developmental toxicants exert effects on developing human infants.

In the absence of information concerning the critical period of time in which a developmental toxicant may exert its effects and given the vulnerability of the potentially affected population (i.e. human infants), it is reasonable to assume that *any* exposure may result in undesirable effects. EPA's *Guidelines for Developmental Toxicity Risk Assessment*, (Federal Register, 12/5/91) as well as EPA's *Risk Assessment Guidance for Superfund, Volume I, Part A* (EPA/540/1-89/002) indicate that assessment of the risks of exposure to developmental toxicants should be based on a daily dose *that is not adjusted for duration or pattern of exposure.* Part 201 cleanup criteria for developmental toxicants including TCDD and related compounds are, therefore, based on a single exposure event for a pregnant 62 Kg adult female under all land use categories.

**Part 201 Cleanup Direct Contact Criteria for Soils**

Section 20120a(4) states, "If a hazardous substance poses a risk of both cancer and 1 or more adverse health effects other than cancer, cleanup criteria shall be derived under this section for the most sensitive effect." Part 201 soil direct contact criteria (DCC) for TCDD and related compounds are given below.

| | Noncarcinogenic Effects | Carcinogenic Effects |
|---|---|---|
| Residential Land Use | 0.27 ug/Kg | 0.23 ug/Kg |
| Industrial Land Use | 0.36 ug/Kg | 2.1 ug/Kg |

The following equation is used to calculate residential DCC for TCDD based on carcinogenic effects:

$$DCC = \frac{10^{-5} \times AT \times CF}{SF \times [(EF_i \times IF \times AE_i) + (EF_d \times DF \times AE_d)]}$$

where,

| | |
|---|---|
| DCC (direct contact criterion) | = ug/kg (ppb) |
| $10^{-5}$ cancer risk | = target risk |
| AT (averaging time) | = 25,550 days (70 x 365) |
| CF (conversion factor) | = 1E+9 ug/kg |
| SF (cancer slope factor) | = 4.9E+4 $(mg/kg\text{-}d)^{-1}$ |
| $EF_i$ (ingestion exposure frequency) | = 350 days/yr |
| IF (age-adjusted soil ingestion factor) | = 114 mg-yr/kg-day |
| $AE_i$ (ingestion absorption efficiency) | = 0.5 (50%) (EPA, 1994b) |
| $EF_d$ (dermal exposure frequency) | = 245 days/yr |
| DF (age-adjusted soil dermal factor) | = 369 mg-yr/kg-day |
| $AE_d$ (dermal absorption efficiency) | = 0.03 (3%) (EPA, 1992) |

The age-adjusted ingestion factor and dermal factor are based on the following equations:

$$IF_{soil/age-adj} = \frac{IR_{soil/age1-6} \times ED_{age1-6}}{BW_{age1-6}} + \frac{IR_{soil/adult} \times ED_{adult}}{BW_{adult}}$$

where,

| | |
|---|---|
| $IR_{soil/age\ 1-6}$ (soil ingestion rate) | = 200 mg/day |
| $ED_{age\ 1-6}$ (exposure duration) | = 6 years |
| $BW_{age\ 1-6}$ (body weight) | = 15 kg |
| $IR_{soil/adult}$ (soil ingestion rate) | = 100 mg/d |
| $ED_{adult}$ (exposure duration) | = 24 years |
| $BW_{adult}$ (body weight) | = 70 kg |

$$DF_{soil/age-adj} = \frac{SA_{age1-6} \times AF \times ED_{age1-6}}{BW_{age1-6}} + \frac{SA_{adult} \times AF \times ED_{adult}}{BW_{adult}}$$

where,

| | |
|---|---|
| $SA_{age\ 1-6}$ (skin surface area) | = 2,900 $cm^2$/day (MDEQ, 1999) |
| $AF_{age\ 1-6}$ (soil adherence factor) | = 0.2 $mg/cm^2$ (MDEQ, 1999) |
| $ED_{age\ 1-6}$ (exposure duration) | = 6 years |
| $BW_{age\ 1-6}$ (body weight) | = 15 kg |
| $SA_{adult}$(skin surface area) | = 5,700 $cm^2$/day (MDEQ, 1999) |
| $AF_{adult}$ (soil adherence factor) | = 0.07 $mg/cm^2$ (MDEQ, 1999) |
| $ED_{adult}$ (exposure duration) | = 24 years |
| $BW_{adult}$ (body weight) | = 70 kg |

The following equation is used to calculate DCC for TCDD based on carcinogenic effects for industrial land use:

$$DCC = \frac{10^{-5} \times BW \times AT \times CF}{SF \times ED \times [(EF_i \times IR_s \times AE_i) + (EF_d \times SA \times AF \times AE_d)]}$$

where,

| | |
|---|---|
| DCC (direct contact criterion) | = ug/kg (ppb) |
| $10^{-5}$ cancer risk | = target risk |
| BW (body weight) | = 70 kg |
| AT (averaging time) | = 25,550 days |
| CF (conversion factor) | = 1E+9 ug/kg |
| SF (cancer slope factor) | = 4.9E+4 $(mg/kg\text{-}day)^{-1}$ |
| ED (exposure duration) | = 21 years |
| $EF_i$ (ingestion exposure frequency) | = 245 days/yr |
| $IR_s$ (soil ingestion rate) | = 50 mg/day |
| $AE_i$ (ingestion absorption. efficiency) | = 0.5 (50%) (EPA, 1994b) |
| $EF_d$ (dermal exposure frequency) | = 112 days/yr |
| SA (skin surface area) | = 3,300 $cm^2$/day (MDEQ, 1999) |
| AF (soil adherence factor) | = 0.2 $mg/cm^2$ (MDEQ, 1999) |
| $AE_d$ (dermal absorption efficiency) | = 0.03 (3%) (EPA, 1992) |

Part 201 residential DCC protective of noncarcinogenic developmental effects are calculated using the following equation:

$$DCC = \frac{HQ \times RfD \times BW \times AT \times RSC \times CF}{EF \times ED \times (IR_S \times AE_i) + (SA \times AF \times AE_d)]}$$

where,

| | |
|---|---|
| DCC (direct contact criterion) | = ug/kg (ppb) |
| HQ (hazard quotient) | = 1 |
| RfD (oral reference dose) | = 1E-9 mg/Kg-day |
| BW (body weight) | = 62 Kg (adult female) |
| AT (averaging time) | = 1 day |
| RSC (relative source contribution) | = 0.2 (20%) |
| CF (conversion factor) | = 1E+9 ug/kg |
| EF (exposure frequency) | = 1 day/yr |
| ED (exposure duration) | = 1 year |
| $IR_s$ (soil ingestion rate) | = 100 mg-yr/kg-day |
| $AE_i$ (ingestion absorption efficiency) | = 0.5 (50%) (EPA, 1994b) |
| SA (surface area) | = 5,120 (EPA, 1997a) |
| $AE_d$ (dermal absorption efficiency) | = 0.03 (3%) (EPA, 1992) |

The equation above is used to calculate the industrial DCC protective of developmental effects by substituting the following exposure assumption to characterize an adult female under the industrial scenario.

| | |
|---|---|
| DCC (direct contact criterion) | = ug/kg (ppb) |
| HQ (hazard quotient) | = 1 |
| RfD (oral reference dose) | = 1E-9 mg/Kg-day |
| BW (body weight) | = 62 Kg (adult female) |
| AT (averaging time) | = 1 day |
| RSC (relative source contribution) | = 0.2 (20%) |
| CF (conversion factor) | = 1E+9 ug/kg |
| EF (exposure frequency) | = 1 day/yr |
| ED (exposure duration) | = 1 year |
| $IR_s$ (soil ingestion rate) | = 50 mg-yr/kg-day |
| $AE_i$ (ingestion absorption efficiency) | = 0.5 (50%) (EPA, 1994b) |
| SA (surface area) | = 3,300 (MDEQ, 1999) |
| $AE_d$ (dermal absorption efficiency) | = 0.03 (3%) (EPA, 1992) |

A comparison of the DCC for noncarcinogenic and carcinogenic effects indicates that, for non-residential land use, the DCC protective of developmental effects is more restrictive than the DCC protective of carcinogenic effects. The DCC for industrial land use is, therefore, 0.36 ug/Kg. The residential DCC is 0.23 ug/Kg based on protection for carcinogenic effects. Since Part 201 criteria for all other soil exposure pathways are less restrictive than the DCC, the DCC become the controlling criteria to address contaminated soils under Part 201.

Part 201 Drinking Water Criteria for Groundwater

Per section 324.20120a(5) of Part 201 of Act 451, the Part 201 drinking water criteria for all land uses is the state drinking water standard of 3.0E-5 ug/L established pursuant to section 5 of the Safe Drinking Water Act (399 PA 1976).

UNCERTAINTY

Alternative methods for extrapolation of the effective dose from test animals to humans could not be addressed in the development of Part 201 criteria for TCDD and related compounds. The traditional approach used in the development of Part 201 criteria is to express dose for both humans and the test specie as a daily intake in mg chemical per Kg body weight per day (mg/Kg/day). This approach may not be appropriate for assessing the risks of TCDD and other bioaccumulative toxicants due to the relatively long biological half-life of TCDD and other chemicals in humans as compared to test animals (DeVito et al, 1995; Grassman et al, 1998).

The half-life is a measure of rate for the time required to eliminate one half of a quantity of a chemical from the body. If a consistent repeated dose of a chemical exceeds the quantity eliminated within the same time span, the chemical builds up or *bioaccumulates* within the body tissues. A steady state *body burden* is reached when the intake dose/time equals elimination/time without appreciable change in the accumulated concentration of a chemical in the body tissues. For bioaccumulative compounds such as TCDD, the steady state body burden may be more critical than daily dose in producing adverse effects. Comparisons of effective dose levels of TCDD across species based on daily intakes frequently results in dose ranges that span several orders of magnitude. When these effective dose levels are converted to body burdens, for most effects including cancer and developmental effects, the differences in effective dose between species are much smaller (DeVito, 1995; Grassman, 1998). The steady state body burden may be, therefore, a more pertinent standard of measurement than a daily dose of bioaccumulative compound when extrapolating from test animals to humans.

TCDD exhibits a much shorter half-life in animal models (e.g., 10-31 days for rodents (U.S. EPA, 1997; Grassman et al, 1998), 144-788 days for female rhesus monkeys (Bowman et al, 1989)) as compared to humans (2118-5150 days) (U.S. EPA, 1997; Grassman et al, 1998). Therefore, the human body burden will be higher than a test species body burden when both humans and animals are exposed to the same daily dose, and the actual risk to humans may be greater than would be predicted based solely on extrapolation of a daily dose. For example, it is estimated that the human body burden would be approximately 5-7 times the monkey body burden at steady state given the same daily dose (DeVito, 1999). Adverse effects in humans may therefore become evident at lower daily doses than those administered to monkeys in studies of TCDD.

EPA has suggested that assessing the steady state body burden concentration to extrapolate from one animal species to another is the appropriate approach for chronic effects and assessing the peak body burden concentration is appropriate for developmental effects (EPA, 1997). However, there is no guidance from EPA on how to assess the risk of the noncancer effects based on the body burden or peak body burden. Pharmacokinetic models have been used to convert test animal data into target tissue concentration in extrapolating from rodent species to humans for female liver cancer risk estimates, however, similar models have not been developed for extrapolating from rhesus monkeys to humans for the most sensitive noncancer endpoints (EPA, 1997). In the absence of EPA guidance to address this issue, this concern cannot be incorporated into the development of Part 201 criteria at this time. Methods to address these concerns will be incorporated if they become available in the future.

Another concern is the protectiveness of the Part 201 criteria for young children who may be more susceptible to the effects of TCDD and related compounds than adults. The precise dose to the developing fetus and/or the dose to lactating infants could not be determined from the Schantz et. al. (1992) study. However, since TCDD tends to concentrate in breast milk, it may be assumed that the nursing infants received a higher dose than that administered to the adult female monkey. It is not possible at this time to calculate Part 201 criteria based solely on a

child receptor. However, since the DCC given above have been developed to be protective of a developing human fetus they are presumed to be protective of young children as well. Information that addresses children's susceptibility to TCDD will be incorporated into Part 201 criteria development if it becomes available in the future.

## TOXIC EQUIVALENCY FACTORS

The EPA has established a toxic equivalency approach for estimating the risks of exposures to TCDD-related compounds (EPA, 1989). Originally this approach was approved by the EPA in 1987, but was modified in 1989 to be consistent with the recommendations of the North Atlantic Treaty Organization's Committee on Challenges of Modern Society (NATO/CCMS) (EPA, 1989). The current approach is based on data from studies where dosed animal groups received either TCDD or other related compounds. The type and severity of effects could therefore be noted separately for each congener or related compound, permitting comparison of the potency of each to TCDD. While the dose necessary to produce a toxic effect may differ from one effect to another, the relative potency of the different congeners compared to TCDD remains fairly constant. Since it has been demonstrated that many of the effects observed are mediated by the Ah receptor, it may be concluded that the potency of TCDD and related compounds in producing these effects may be attributed, at least in part, to the relative binding affinity of these compounds to the Ah receptor (EPA, 1994b; ATSDR, 1998; Birnbaum, 1995). Therefore, the TEFs may be used to assess the risk of a variety of toxic effects associated with exposure to TCDD and related compounds.

Under the 1989 international approach adopted by EPA, a toxic equivalency factor (TEF) is assigned to each dioxin and furan congener. TEFs range from zero (0) to one (1), where 0 represents no TCDD-like toxicity and one represents toxicity of equal potency to TCDD. The concentration of each congener in the affected media is multiplied by its respective TEF to determine its TCDD equivalent concentration and the products are summed to obtain the total TCDD concentration in the media sample. The total TCDD toxic equivalency (TEq) is used as the concentration term in risk assessments or as the concentration to be compared to the Part 201 generic criteria for 2,3,7,8-TCDD. An inherent assumption of this approach is that TCDD-related effects produced via Ah receptor mediated mechanism are additive.

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4/19 Draft

DRAFT DELIBERATIVE PROCESS

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY (MDEQ)
ENVIRONMENTAL RESPONSE DIVISION (ERD)

# TOXICOLOGICAL ASSESSMENT AND PART 201 CLEANUP CRITERIA FOR 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN AND RELATED COMPOUNDS

April 25, 2002
TSG Dioxin Subcommittee

This document presents the Part 201 Toxicological Assessment (TA) for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds. This review will only address the toxicity of TCDD related to the oral route of exposure. This TA does not address inhalation exposures to TCDD or TCDD-related compounds. The oral cancer slope factor and reference dose presented in the following discussion are assumed to be applicable to the dermal route of exposure.

Drinking water criteria for TCDD and related compounds are not calculated from the oral cancer slope factor and reference dose presented in the following discussion. Per section 324.20120a(5) of Part 201 of Act 451, the Part 201 drinking water criteria for TCDD for all land uses is the state drinking water standard of 3.0E-5 ug/L established pursuant to section 5 of the Safe Drinking Water Act (399 PA 1976).

## EXECUTIVE SUMMARY *revise this when rest of TA is done*

TCDD and related compounds have been shown to cause a wide variety of adverse effects in experimental animals and in exposed human populations. Observed effects in experimental animals are diverse and include lethality, cancer, immunotoxicity, hepatotoxicity, dermal toxicity, endocrine disruption, reproductive and developmental effects, and enzyme induction. Many of these effects have been observed in human populations exposed to TCDD and related compounds in occupational settings or through accidental release to the environment. Part 201 of Act 451 requires that cleanup criteria be developed to be protective of the most sensitive effect considering cancer and noncancer effects. The current MDEQ review focuses on carcinogenicity and the three noncarcinogenic endpoints identified as the most sensitive for TCDD and related compounds: hepatotoxicity (liver toxicity), immunotoxicity (adverse effects in the immune system), and reproductive/developmental toxicity. Developmental neurobehavioral alterations in rhesus monkeys occurs at lower daily doses than either hepatotoxicity or immunotoxicity and is, therefore, the most sensitive noncarcinogenic effect.

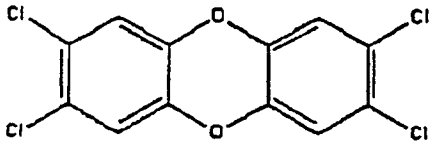
A comparison of the Part 201 soil direct contact criteria (DCC) protective of cancer to the DCC protective of developmental neurobehavioral effects indicates that the most sensitive effect differs for residential and non-residential land uses. For residential land use, the DCC will be based on protection for carcinogenic effects: the Part 201 generic residential DCC is 0.23 ug/Kg. For non-residential land use, the DCC will be based on protection for noncarcinogenic developmental neurobehavioral effects: the Part 201 generic industrial DCC is 0.36 ug/Kg. Part 201 generic commercial DCC will be developed at a later date. The most sensitive effect differs between land uses because the generic exposure assumptions used to calculate DCC differ between residential and non-residential land uses. The Part 201 drinking water criteria for all land uses is the state drinking water standard of 3.0E-5 ug/L per section 324.20120a(5) of Part 201 of Act 451.

## INTRODUCTION

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is the representative prototype of a class of structurally related compounds that are ubiquitous and persistent in the environment. The basic

structure of these compounds is a double benzene ring joined at the *para* carbon positions with 2 oxygen atoms. Halogens, generally either chlorine or bromine, may be substituted at the four remaining carbon positions on each benzene ring. Monohalogenated through octahalogenated congeners of the dibenzo-p-dioxins are therefore possible. Research into the toxic effects of these compounds has focused primarily on congeners with halogens at the four lateral carbon positions. 2,3,7,8-Tetrachlorodibenzo-p-dioxin or TCDD, with all four lateral positions occupied by chlorine, is considered the most toxic of the dibenzo-p-dioxins and related compounds. The toxicity of other dibenzo-p-dioxins, related compounds such as dibenzo-p-furans and coplanar polychlorinated biphenyls are assessed relative to the potency of TCDD (ATSDR, 1998).

The chemical structure of TCDD is shown below.




The toxicity of TCDD and related compounds has been extensively reviewed by the Environmental Protection Agency (EPA), Office of Research and Development, the U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR), and the World Health Organization (WHO). EPA has released its findings in a three part "draft final" multi-volume document entitled "Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds". The three parts are as follows: "Part I: Estimating Exposure to Dioxin-Like Compounds (EPA 2000a); "Part II: Health Assessment for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds (EPA 2000b); and "Part III: Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds (EPA 2000c). A final version of the Dioxin Reassessment has not yet been released. ATSDR's review is contained in the updated "Toxicological Profile for Chlorinated Dibenzo-p-Dioxins" (ATSDR, 1998). The ATSDR profile is considered final. In 1998, forty international experts in the field of toxicology met in Geneva, Switzerland to revise the WHO tolerable daily intake (TDI) for dioxins (WHO, 1998). In addition, a joint FAO/WHO Committee on Food Additives conducted a meeting in June 2001 where dioxins were discussed in depth (FAO/WHO, 2001). Other documents evaluated by the subcommittee include three documents written by ATSDR scientists (DeRosa et al., 1997a; DeRosa et al., 1997b; Pohl et al., 2002). The following MDEQ review relies primarily on these documents, supplemented by original key studies from the scientific literature as necessary.

TCDD and related compounds have been shown to cause a wide variety of effects in experimental animals and in exposed human populations. Observed effects in experimental animals are diverse and include lethality, cancer, immunotoxicity, hepatotoxicity, dermal toxicity, endocrine disruption, reproductive and developmental effects, and enzyme induction. Information on human health effects comes from occupational exposures or from populations exposed due to accidental releases or contamination of the food supply. Human studies are difficult to interpret due to incomplete information regarding dose, concomitant exposure to other compounds, and the limited number of people exposed (ATSDR, 1998). Therefore, the remainder of this review will focus on effects observed in experimental animals. However, preliminary data obtained from the study of exposed human populations indicates that many of the effects noted in experimental animals also occur in humans (Birnbaum, 1995; DeVito et al, 1995; Grassman et al, 1998).

## TOXICOLOGICAL REVIEW

The EPA Dioxin Reassessment and the ATSDR Toxicological Profile provide exhaustive reviews of the available scientific literature reporting on the toxic effects of TCDD. These documents are recommended for additional reading. The current MDEQ review will focus on potential carcinogenicity and the three noncarcinogenic endpoints that have been identified as the most sensitive for TCDD and related compounds: hepatotoxicity (liver toxicity), immunotoxicity (adverse effects in the immune system), and reproductive/developmental toxicity.

### Mechanism of Action

Early investigation into the toxic effects of TCDD yielded seemingly paradoxical results. Effects varied widely between species, between strains of the same test species, and between tissues in the same test animal. Recent research has indicated that the effects of TCDD are mediated through binding to the intracellular protein known as the aryl hydrocarbon (Ah) receptor. Binding of TCDD with the Ah receptor is stereospecific, meaning that only compounds of similar chemical structure and three dimensional configuration will bind to the receptor and produce activation of the responses it mediates (EPA, 1994b). The Ah receptor is believed to be the first step in activation of a group of proteins that regulate mRNA mediated enzyme and protein production in the cell nucleus. The Ah receptor is also believed to function in the cytoplasm as a regulator of second messenger proteins (Birnbaum, 1995). These proteins act as chemical messengers, conveying information from receptor sites near the cell membrane to the nucleus where various cellular support mechanisms are regulated. These cellular functions are intrinsically involved in cell growth, viability, proliferation, differentiation, and cell death. The variation in effects of dioxins across strain and species and even between tissues of the same organism may, therefore, be attributed to genetic and functional variation in the role of the Ah receptor and the diversity of the responses it mediates.

### Carcinogenicity

TCDD has been shown to be a multisite carcinogen in mice and rats in several chronic bioassays for carcinogenicity, the most important of which are the Kociba et al. (1978) and National Toxicology Program (1982) studies. Carcinogenicity has also recently been demonstrated in the hamster, considered to be the most resistant species to the acute toxic effects of TCDD (EPA, 2000). The Kociba 1978 assay in Sprague-Dawley rats is the basis for the oral carcinogenic slope factor calculated by EPA and MDEQ and is summarized below.

Kociba et al. (1978) administered TCDD to 50 rats per sex per group in-feed at doses of 0.001, 0.01, and 0.1 ug TCDD/Kg of body weight per day for 2 years. The control group of 86 male and 86 female rats were administered the vehicle alone. The findings of this study relative to carcinogenesis include increases in hepatocellular hyperplastic nodules and hepatocellular carcinomas in female rats, squamous cell carcinomas of the nasal turbinates, hard palate and tongue in male rats, and lung tumors in high-dose female rats. The liver tumor incidence in female rats was significantly elevated above control animals at the 0.01 ug TCDD/Kg dose level and showed clear evidence of a dose-response relationship. Lung tumors in female rats were significantly elevated in the high-dose group. The increased incidence of squamous cell carcinomas of the nasal turbinates, hard palate and tongue in male rats was significant in the low-dose group, but no evidence of a dose-response relationship was apparent. Liver and lung tumors were not observed in male rats.

In 1990 an independent panel of seven pathologists under the direction of the U.S. Food and Drug Administration and the EPA, reevaluated the female liver slides according to the National Toxicology Program's 1986 liver tumor classification scheme. These results, combined with the previously noted incidences of lung tumors in female rats and tumors of the nasal turbinates, hard palate and tongue in male rats, formed the basis for the oral slope factor of 7.5E+4

$(mg/Kg\text{-}day)^{-1}$ previously developed by MDEQ (MDEQ, 1990). This value is derived from the calculated animal cancer potency value from the Kociba study (1978) using the linear multistage (LMS) cancer model. The animal cancer potency value was multiplied by a species scaling factor of the human body weight to the test species weight raised to the 3/4 power to account for the differences between humans and test species. The oral slope factor based on the combined tumor incidence rate observed from Kociba (1978) and a ¾ power species scaling factor is 4.9E+4 $(mg/Kg\text{-}day)^{-1}$.

Noncarcinogenic Effects of TCDD

Three noncarcinogenic endpoints have been identified by EPA, ATSDR, and WHO as the most sensitive for TCDD and related compounds: hepatotoxicity (liver toxicity), immunotoxicity (adverse effects in the immune system), and reproductive/developmental toxicity. Observed adverse effects and the key study chosen for the development of an oral references dose (RfD) for each endpoint are discussed below.

Hepatotoxicity

Numerous systemic effects have been noted following oral administration of TCDD to experimental animals. Effects observed include increased mortality, focal alveolar hyperplasia in the respiratory system, myocardial degeneration, hematological changes, renal effects, toxic hepatitis, hepatocellular alterations and hepatic necrosis, dermatitis, and decreased body weight gain. Of these, hepatotoxicity appears to be the most sensitive effect.

The Kociba (1978) study discussed above is the basis for the oral reference dose for hepatotoxic effects. Increased mortality was seen in high dose females, but not in high dose males or in either males or females at lower dose levels. Mean body weights decreased for all high-dose animals from month 6 to the end of the study. Decreased body weight was also observed in mid-dose females, but to a lesser extent. Histological examination of rats surviving to the end of the study indicated multiple degenerative, inflammatory and necrotic changes in the liver. These effects were more extensive in females. Liver damage was dose-related in mid-and high-dose groups, no effects were observable in low-dose groups. The no observed adverse effect level (NOAEL) for hepatotoxicity in this study is 0.001 ug/Kg-day or 1.0E-6 mg/Kg-day.

Immunotoxicity

The database describing the immunotoxic effects of TCDD and related compounds is extensive. High doses of TCDD have been shown to produce atrophy of the thymus. Effects at lower doses include: suppression of T-cell immunity, delayed hypersensitivity responses, increased susceptibility to infectious disease, and alterations in immune effector functions. The available database, however, is not adequate to provide the basis for cross species comparability of effects and dose. Recent advances suggest this is due to variability in the binding affinity of TCDD to the Ah receptor believed to mediate the immunotoxic effects of TCDD. Strains of mice that exhibit genetic differences in Ah receptor function show significant differences in immunosuppresion following administration of TCDD and/or related compounds. In addition, TCDD congeners that show greater binding affinity for the Ah receptor have been shown to be more potent in eliciting immunosuppressive responses than congeners with relatively less affinity for the Ah receptor.

RfD for Immunotoxicity – Thymic atrophy was observed in high-dose rats in Kociba et al. (1978). The NOAEL for this effect is 0.01 ug/Kg/day. Hong et al. (1989) reported immune abnormalities in offspring of rhesus monkeys exposed prenatally and lactationally to TCDD. The test subjects were the same individuals used in the Schantz et al. 1992 study described below. However, the NOAEL identified by ATSDR (1998) for immunotoxicity from this study is inconsistent with the dose levels reported in Schantz et al. (1992). Since Hong reported no

adverse immunotoxic effects in low-dose offspring, it may be concluded that the RfD for developmental effects described below based on the lowest dose administered in the Schantz study is protective of potential immunotoxic effects.

Reproductive /Developmental Toxicity

TCDD administered to experimental animals has been shown to cause adverse effects in both male and female reproductive symptoms. Effects observed in females include: decreases in ovarian weight, altered estrus cycle and ovulation, pre- and post-implantation fetal loss, reduced fertility, and alterations in levels of circulating hormones. Effects observed in males include: decreased testis and accessory organ weights, abnormal testicular morphology, decreased spermatogenesis, reduced fertility, and reduced levels of androgenic hormones. Developmental effects in offspring of TCDD exposed female animals include: mortality; structural malformations such as cleft palate and hydronephrosis; thymic atrophy; immunosuppression; structural and functional impairment of the reproductive system including decreased spermatogenesis; decreased weight of the urogenital system in male offspring including the ventral prostate, intestinal, subcutaneous and brain hemorrhages; decreased growth; and neurobehavioral alterations. Effects in offspring occurred following TCDD administration to dams prior to mating, during gestation, and during lactation. Fetal death has occurred in several experimental animals, including monkeys, at doses that caused no apparent maternal toxicity. Structural defects in mice have been observed at doses that caused no apparent maternal or fetal toxicity. Of these observed effects, neurobehavioral alterations in rhesus monkeys (Schantz et al., 1992) is the most sensitive and was used by ATSDR to develop a chronic minimal risk level (MRL) of 1.0E-9 mg/Kg-day for daily human exposure.

Pregnant Holtzman rats were given a single oral dose of TCDD at 0-0.8 ug/kg/ bw on day 15 of gestation (Ohsako et al., 2001). Male offspring were examined on days 49 and 120 after birth. The weight of the urogenital complex, including the ventral prostate, was significantly reduced at doses of 0.2 and 0.8 ug/kg. The anogenital distance of male rats receiving doses of 0.05 ug/kg or above was significantly decreased. No effects were seen at the lowest dose of 0.0125 ug/kg. The equivalent maternal body burden after multiple doses at this NOEL would be 0.013 ug/kg.

Another recent study treated Wistar rat dams subcutaneously prior to mating and throughout mating, pregnancy and lactation (Faqi et al., 1998). The initial dose of 0.025, 0.060 or 0.300 ug TCDD/kg body weight was administered 2 weeks prior to mating. Weekly maintenance doses of 0.005, 0.012, or 0.060 ug TCDD/kg followed the initial loading dose. Effects on male reproduction were studied on postnatal days 70 and 170. The number of sperm per cauda epididymis was reduced in all treated groups at puberty and adulthood. In addition, the male offspring of the treated groups showed an increased number of abnormal sperm when investigated at adulthood. A maternal body burden of 0.025 ug TCDD/kg at steady state would be needed to produce the total fetal body burden.

Schantz et al. (1992) administered TCDD to groups of eight rhesus monkeys at doses of 0, 5, and 25 part per trillion (ppt) in-feed for a total of 16.2±0.4 months. Monkeys were mated after 7 months of exposure to an unexposed male. Seven of eight high-dose monkeys failed to deliver viable offspring, therefore, only offspring on the 5 ppt group were available for behavioral studies. TCDD administration continued throughout gestation and lactation. Offspring were weaned at age 4 months. At 8.6 months of age, offspring were placed in peer groups of two dosed and two control monkeys. Behavioral patterns in a play room were observed for 1.5 hours per day, 4 days per week for 9 weeks. Significant alterations were observed in play behavior, displacement behavior, and self-directed behavior in the dosed offspring as compared to controls. Dosed offspring tended to initiate rough play more often, to retreat from rough play less often, and were less often displaced from preferred positions in the play area. Dosed offspring also tended to engage in self-directed behavior more often than controls. This

behavior is defined as oral, manual or pedal self-manipulation and is considered to be a maladaptive behavioral pattern. This pattern of behavior is characteristic of monkeys reared in conditions of social deprivation and is consistent with a similar pattern of behavior in emotionally disturbed human children. The authors postulated that the observed increase in both adaptive and maladaptive social behaviors may be indicative of an increase in the overall level of behavioral arousal.

*Revise based on new recommendations:*
**Developmental RfD** - A NOAEL could not be identified for the Schantz et al. (1992) study. The lowest observed adverse effect level (LOAEL) of 5 ppt is converted to 1.3E-4 ug/Kg-day (1.3E-7 mg/Kg-day) using the food consumption rate of 0.19 kg/day (Schantz et al. 1992) and a maternal body weight of 7.5 kg (Bowman et al. 1989). A $10^{0.5}$ UF is applied to account for the use of a minimal LOAEL since the observed neurobehavioral effects are not of marked severity. A $10^{0.5}$ UF is applied for extrapolation from monkeys to humans. A full10-fold factor for interspecies extrapolation is not considered necessary because of similarities in toxic responses and general physiology between monkeys and humans. An additional UF of 10 is applied to account for sensitive human individuals. Application of the total UF of 100 ($10^{0.5}$ x $10^{0.5}$ x 10) yields an oral RfD of 1.3E-9 mg/kg-day.

The total UF of 100 used to develop the RfD for Part 201 criteria calculations differs from the UF of 90 presented in the ATSDR Toxicological Profile. ATSDR used UFs of 3 for use of a minimal LOAEL, 3 for interspecies extrapolation, and 10 to account for sensitive human individuals. The use of a 3-fold UF is not consistent with the logarithmic basis of uncertainty factor development. Therefore, the more appropriate value of $10^{0.5}$, rather than 3, has been used here to represent the mid-point between 1 and 10 on a logarithmic scale (Dourson, 1994; Swartout, 1999).

## BACKGROUND EXPOSURES

Chapter 5 of Estimating Exposure to Dioxin-Like Compounds (EPA, 1994a) provides an assessment of background exposures to TCDD and related compounds. This assessment uses national average concentrations of TCDD and related compounds in air, drinking water, soil, and in the food supply to estimate the background levels to which U.S. citizens may be exposed. Intake rates for food products were estimated using data from the U.S. Department of Agriculture's (USDA) report on "Food Consumption, Prices, and Expenditures between 1970 and 1992" and the USDA's "National Food Consumption Survey" (1992). Food products considered include milk, dairy, eggs, beef, pork and poultry. This study indicates that the average U.S. citizen is exposed via these food products to approximately 110 picograms of TCDD and related compounds per day (1.6 pg/kg of body weight/day assuming a 70 Kg adult).

The estimated background value of 1.6 pg/kg/day given above falls roughly at the mid-point of the range of 0.3 pg/kg/day to 3.0 pg/Kg/day (18-192 pg/day) for daily intake rates reported by Schecter et al. (1994). Schecter used a concentration range of TCDD and related compounds in foods purchased in New York state rather than an average concentration to calculate the levels to which a 65 kg adult may be exposed. While only foods purchased in New York were used in this study, the results may be generally applicable since food supplies in the U.S. may be shipped long distances and most major brands are marketed nationally. The concentration range used in this study may be preferable to the averaging technique used by EPA (1994a). In the EPA study, samples with no detectable TCDD or related compounds were reported for the purposes of averaging to have concentrations at the detection limit of the analysis. This approach may be faulty since the data are insufficient to conclude that all food products of the type sampled will contain some, albeit undetected, level of TCDD or related compounds.

Section 20120a(4) of Part 201 of Act 451 states, "For the noncarcinogenic effects of a hazardous substance present in soils, the intake shall be assumed to be 100% of the protective

level, unless compound and site-specific data are available to demonstrate that a different source contribution is appropriate." The above discussion indicates that TCDD and related compounds are present in nationally available food products that are commonly consumed on a daily basis by the average U.S. citizen. However, the data are insufficient at this time to more precisely predict the levels at which these or other non-soil exposures may occur. It is therefore assumed that 80% of the average exposure to TCDD and related compounds occurs from a source other than exposure to contaminated soils. Therefore, Part 201 soil direct contact criteria for TCDD and related compounds protective of noncarcinogenic effects are calculated employing a 20% relative source contribution factor (RSC).

## EXPOSURE ASSUMPTIONS AND CRITERIA CALCULATION

### Exposure Values for Carcinogenic Effects

For carcinogenic compounds, exposures are calculated by prorating the total cumulative dose over a lifetime of 70 years (also called lifetime average daily dose). The approach for carcinogens is based on the assumption that a high dose of a carcinogen received over a short period of time is equivalent to a corresponding low dose spread over a lifetime. Part 201 residential DCC assume that exposure occurs over a 30 year exposure duration at an exposure frequency of 350 days/year. Intake of soil via the soil incidental ingestion and dermal direct contact pathways is age-adjusted to account for behaviors in children that result in higher exposure. Part 201 industrial DCC assume that exposure occurs over a 21 year exposure duration at an exposure frequency of 245 days/year for ingestion and 112 days/year for dermal contact. Children are not assumed to be present on industrial property.

### Exposure Values for Developmental Effects

The noncarcinogenic Part 201 DCC protective of developmental effects for all land uses are intended to be protective of a pregnant female adult and her developing fetus. The timing of exposure to developmental toxicants may affect both the type and severity of effect on the developing organism. Some compounds may exert these effects after only a single exposure, while others may require a longer period of exposure before effects are manifested. For example, blastocyst formation and implantation occur in 1 to 2 days (day 3-5 post fertilization) in most mammalian species including humans. A single dose of a compound that interferes with these processes may result in arrested development of the embryo and probable lethality. The period of organogenesis during which primitive cells divide and association into organ rudiments typically lasts for several days, ranging from 6-15 days post fertilization in rodents to days 21-56 in humans. During this 35 day period in humans, individual organ systems may be more or less susceptible on any given day and critical periods for each system may show considerable overlap. Structural defects are often the result of exposure during this time, but functional effects may also be noted. Growth retardation and functional impairment may also result from exposure during the fetal and neonatal period following organogenesis. Unfortunately, little is known about the critical period during which most developmental toxicants exert effects on developing human infants.

In the absence of information concerning the critical period of time in which a developmental toxicant may exert its effects and given the vulnerability of the potentially affected population (i.e. human infants), it is reasonable to assume that *any* exposure may result in undesirable effects. EPA's *Guidelines for Developmental Toxicity Risk Assessment*, (Federal Register, 12/5/91) as well as EPA's *Risk Assessment Guidance for Superfund, Volume I, Part A* (EPA/540/1-89/002) indicate that assessment of the risks of exposure to developmental toxicants should be based on a daily dose *that is not adjusted for duration or pattern of exposure*. Part 201 cleanup criteria for developmental toxicants including TCDD and related compounds are, therefore, based on a single exposure event for a pregnant 62 kg adult female under all land use categories.

Part 201 Cleanup Direct Contact Criteria for Soils

Section 20120a(4) states, "If a hazardous substance poses a risk of both cancer and 1 or more adverse health effects other than cancer, cleanup criteria shall be derived under this section for the most sensitive effect." Part 201 soil direct contact criteria (DCC) for TCDD and related compounds are given below.

| | Noncarcinogenic Effects | Carcinogenic Effects |
|---|---|---|
| Residential Land Use | | |
| Industrial Land Use | | |

The following equation is used to calculate residential DCC for TCDD based on carcinogenic effects:

$$DCC = \frac{10^{-5} \times AT \times CF}{SF \times [(EF_i \times IF \times AE_i) + (EF_d \times DF \times AE_d)]}$$

where,

| | |
|---|---|
| DCC (direct contact criterion) | = ug/kg (ppb) |
| $10^{-5}$ cancer risk | = target risk |
| AT (averaging time) | = 25,550 days (70 x 365) |
| CF (conversion factor) | = 1E+9 ug/kg |
| SF (cancer slope factor) | = 4.9E+4 $(mg/kg\text{-}d)^{-1}$ |
| $EF_i$ (ingestion exposure frequency) | = 350 days/yr |
| IF (age-adjusted soil ingestion factor) | = 114 mg-yr/kg-day |
| $AE_i$ (ingestion absorption efficiency) | = 0.5 (50%) (EPA, 1994b) |
| $EF_d$ (dermal exposure frequency) | = 245 days/yr |
| DF (age-adjusted soil dermal factor) | = 369 mg-yr/kg-day |
| $AE_d$ (dermal absorption efficiency) | = 0.03 (3%) (EPA, 1992) |

The age-adjusted ingestion factor and dermal factor are based on the following equations:

$$IF_{soil/age-adj} = \frac{IR_{soil/age1-6} \times ED_{age1-6}}{BW_{age1-6}} + \frac{IR_{soil/adult} \times ED_{adult}}{BW_{adult}}$$

where,

| | |
|---|---|
| $IR_{soil/age\ 1\text{-}6}$ (soil ingestion rate) | = 200 mg/day |
| $ED_{age\ 1\text{-}6}$ (exposure duration) | = 6 years |
| $BW_{age\ 1\text{-}6}$ (body weight) | = 15 kg |
| $IR_{soil/adult}$ (soil ingestion rate) | = 100 mg/d |
| $ED_{adult}$ (exposure duration) | = 24 years |
| $BW_{adult}$ (body weight) | = 70 kg |

$$DF_{soil/age-adj} = \frac{SA_{age1-6} \times AF \times ED_{age1-6}}{BW_{age1-6}} + \frac{SA_{adult} \times AF \times ED_{adult}}{BW_{adult}}$$

where,

| | |
|---|---|
| $SA_{age\ 1\text{-}6}$ (skin surface area) | = 2,900 $cm^2$/day (MDEQ, 1999) |
| $AF_{age\ 1\text{-}6}$ (soil adherence factor) | = 0.2 mg/$cm^2$ (MDEQ, 1999) |
| $ED_{age\ 1\text{-}6}$ (exposure duration) | = 6 years |
| $BW_{age\ 1\text{-}6}$ (body weight) | = 15 kg |
| $SA_{adult}$(skin surface area) | = 5,700 $cm^2$/day (MDEQ, 1999) |
| $AF_{adult}$ (soil adherence factor) | = 0.07 mg/$cm^2$ (MDEQ, 1999) |
| $ED_{adult}$ (exposure duration) | = 24 years |
| $BW_{adult}$ (body weight) | = 70 kg |

The following equation is used to calculate DCC for TCDD based on carcinogenic effects for industrial land use:

$$DCC = \frac{10^{-5} \times BW \times AT \times CF}{SF \times ED \times [(EF_i \times IR_s \times AE_i) + (EF_d \times SA \times AF \times AE_d)]}$$

where,

| | |
|---|---|
| DCC (direct contact criterion) | = ug/kg (ppb) |
| $10^{-5}$ cancer risk | = target risk |
| BW (body weight) | = 70 kg |
| AT (averaging time) | = 25,550 days |
| CF (conversion factor) | = 1E+9 ug/kg |
| SF (cancer slope factor) | = 4.9E+4 $(mg/kg\text{-}day)^{-1}$ |
| ED (exposure duration) | = 21 years |
| $EF_i$ (ingestion exposure frequency) | = 245 days/yr |
| $IR_s$ (soil ingestion rate) | = 50 mg/day |
| $AE_i$ (ingestion absorption. efficiency) | = 0.5 (50%) (EPA, 1994b) |
| $EF_d$ (dermal exposure frequency) | = 112 days/yr |
| SA (skin surface area) | = 3,300 $cm^2$/day (MDEQ, 1999) |
| AF (soil adherence factor) | = 0.2 mg/$cm^2$ (MDEQ, 1999) |
| $AE_d$ (dermal absorption efficiency) | = 0.03 (3%) (EPA, 1992) |

Part 201 residential DCC protective of noncarcinogenic developmental effects are calculated using the following equation:

$$DCC = \frac{HQ \times RfD \times BW \times AT \times RSC \times CF}{EF \times ED \times (IR_S \times AE_i) + (SA \times AF \times AE_d)]}$$

where,

| | |
|---|---|
| DCC (direct contact criterion) | = ug/kg (ppb) |
| HQ (hazard quotient) | = 1 |
| RfD (oral reference dose) | = 1.3E-9 mg/Kg-day |
| BW (body weight) | = 62 Kg (adult female) |
| AT (averaging time) | = 1 day |
| RSC (relative source contribution) | = 0.2 (20%) |
| CF (conversion factor) | = 1E+9 ug/kg |
| EF (exposure frequency) | = 1 day/yr |
| ED (exposure duration) | = 1 year |
| $IR_s$ (soil ingestion rate) | = 100 mg-yr/kg-day |
| $AE_i$ (ingestion absorption efficiency) | = 0.5 (50%) (EPA, 1994b) |
| SA (surface area) | = 5,120 (EPA, 1997a) |
| AF (soil adherence factor) | = 0.07 mg/$cm^2$ (MDEQ, 1999) |
| $AE_d$ (dermal absorption efficiency) | = 0.03 (3%) (EPA, 1992) |

The equation above is used to calculate the industrial DCC protective of developmental effects by substituting the following exposure assumption to characterize an adult female under the industrial scenario.

| | |
|---|---|
| DCC (direct contact criterion) | = ug/kg (ppb) |
| HQ (hazard quotient) | = 1 |
| RfD (oral reference dose) | = 1.3E-9 mg/Kg-day |
| BW (body weight) | = 62 Kg (adult female) |
| AT (averaging time) | = 1 day |
| RSC (relative source contribution) | = 0.2 (20%) |
| CF (conversion factor) | = 1E+9 ug/kg |
| EF (exposure frequency) | = 1 day/yr |
| ED (exposure duration) | = 1 year |
| $IR_s$ (soil ingestion rate) | = 50 mg-yr/kg-day |
| $AE_i$ (ingestion absorption efficiency) | = 0.5 (50%) (EPA, 1994b) |
| SA (surface area) | = 3,300 (MDEQ, 1999) |
| AF (soil adherence factor) | = 0.2 mg/cm$^2$ (MDEQ, 1999) |
| $AE_d$ (dermal absorption efficiency) | = 0.03 (3%) (EPA, 1992) |

A comparison of the DCC for noncarcinogenic and carcinogenic effects indicates that, for non-residential land use, the DCC protective of developmental effects is more restrictive than the DCC protective of carcinogenic effects. The DCC for industrial land use is, therefore, 0.36 ug/Kg. The residential DCC is 0.23 ug/Kg based on protection for carcinogenic effects. Since Part 201 criteria for all other soil exposure pathways are less restrictive than the DCC, the DCC become the controlling criteria to address contaminated soils under Part 201.

## UNCERTAINTY

Alternative methods for extrapolation of the effective dose from test animals to humans could not be addressed in the development of Part 201 criteria for TCDD and related compounds. The traditional approach used in the development of Part 201 criteria is to express dose for both humans and the test species as a daily intake in mg chemical per Kg body weight per day (mg/Kg/day). This approach may not be appropriate for assessing the risks of TCDD and other bioaccumulative toxicants due to the relatively long biological half-life of TCDD and other chemicals in humans as compared to test animals (DeVito et al, 1995; Grassman et al, 1998).

The half-life is a measure of rate for the time required to eliminate one half of a quantity of a chemical from the body. If a consistent repeated dose of a chemical exceeds the quantity eliminated within the same time span, the chemical builds up or *bioaccumulates* within the body tissues. A steady state *body burden* is reached when the intake dose/time equals elimination/time without appreciable change in the accumulated concentration of a chemical in the body tissues. For bioaccumulative compounds such as TCDD, the steady state body burden may be more critical than daily dose in producing adverse effects. Comparisons of effective dose levels of TCDD across species based on daily intakes frequently results in dose ranges that span several orders of magnitude. When these effective dose levels are converted to body burdens, for most effects including cancer and developmental effects, the differences in effective dose between species are much smaller (DeVito, 1995; Grassman, 1998). The steady state body burden may be, therefore, a more pertinent standard of measurement than a daily dose of bioaccumulative compound when extrapolating from test animals to humans.

TCDD exhibits a much shorter half-life in animal models (e.g., 10-31 days for rodents (U.S. EPA, 1997; Grassman et al, 1998), 144-788 days for female rhesus monkeys (Bowman et al, 1989)) as compared to humans (2118-5150 days) (U.S. EPA, 1997; Grassman et al, 1998). Therefore, the human body burden will be higher than a test species body burden when both

humans and animals are exposed to the same daily dose, and the actual risk to humans may be greater than would be predicted based solely on extrapolation of a daily dose. For example, it is estimated that the human body burden would be approximately 5-7 times the monkey body burden at steady state given the same daily dose (DeVito, 1999). Adverse effects in humans may therefore become evident at lower daily doses than those administered to monkeys in studies of TCDD.

EPA has suggested that assessing the steady state body burden concentration to extrapolate from one animal species to another is the appropriate approach for chronic effects and assessing the peak body burden concentration is appropriate for developmental effects (EPA, 1997). However, there is no guidance from EPA on how to assess the risk of the noncancer effects based on the body burden or peak body burden. Pharmacokinetic models have been used to convert test animal data into target tissue concentration in extrapolating from rodent species to humans for female liver cancer risk estimates, however, similar models have not been developed for extrapolating from rhesus monkeys to humans for the most sensitive noncancer endpoints (EPA, 1997). In the absence of EPA guidance to address this issue, this concern cannot be incorporated into the development of Part 201 criteria at this time. Methods to address these concerns will be incorporated if they become available in the future.

Another concern is the protectiveness of the Part 201 criteria for young children who may be more susceptible to the effects of TCDD and related compounds than adults. The precise dose to the developing fetus and/or the dose to lactating infants could not be determined from the Schantz et. al. (1992) study. However, since TCDD tends to concentrate in breast milk, it may be assumed that the nursing infants received a higher dose than that administered to the adult female monkey. It is not possible at this time to calculate Part 201 criteria based solely on a child receptor. However, since the DCC given above have been developed to be protective of a developing human fetus they are presumed to be protective of young children as well. Information that addresses children's susceptibility to TCDD will be incorporated into Part 201 criteria development if it becomes available in the future.

## TOXIC EQUIVALENCY FACTORS

The EPA has established a toxic equivalency approach for estimating the risks of exposures to TCDD-related compounds (EPA, 1989). Originally this approach was approved by the EPA in 1987, but was modified in 1989 to be consistent with the recommendations of the North Atlantic Treaty Organization's Committee on Challenges of Modern Society (NATO/CCMS) (EPA, 1989). The current approach is based on data from studies where dosed animal groups received either TCDD or other related compounds. The type and severity of effects could therefore be noted separately for each congener or related compound, permitting comparison of the potency of each to TCDD. While the dose necessary to produce a toxic effect may differ from one effect to another, the relative potency of the different congeners compared to TCDD remains fairly constant. Since it has been demonstrated that many of the effects observed are mediated by the Ah receptor, it may be concluded that the potency of TCDD and related compounds in producing these effects may be attributed, at least in part, to the relative binding affinity of these compounds to the Ah receptor (EPA, 1994b; ATSDR, 1998; Bimbaum, 1995). Therefore, the TEFs may be used to assess the risk of a variety of toxic effects associated with exposure to TCDD and related compounds.

Under the 1989 international approach adopted by EPA, a toxic equivalency factor (TEF) is assigned to each dioxin and furan congener. TEFs range from zero (0) to one (1), where 0 represents no TCDD-like toxicity and one represents toxicity of equal potency to TCDD. The concentration of each congener in the affected media is multiplied by its respective TEF to determine its TCDD equivalent concentration and the products are summed to obtain the total TCDD concentration in the media sample. The total TCDD toxic equivalency (TEq) is used as

the concentration term in risk assessments or as the concentration to be compared to the Part 201 generic criteria for 2,3,7,8-TCDD. An inherent assumption of this approach is that TCDD-related effects produced via Ah receptor mediated mechanism are additive.

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